Bayer 253-KGB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: KLAUS GROHE ET AL.
(Patentee's name)

Patent No.: (number) 4,670,444

Issued: (date) June 2, 1987

For: (title) 7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

BOX PATENT EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

LETTER OF TRANSMITTAL OF APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156

Sir:

Transmitted for filing connection with the above-identified patent are the following items:

(1) Application for Extension of Patent Term Under 35 U.S.C. §156;

(2) Attachments A through G thereto;

(3) Declaration Pursuant to 37 C.F.R. §1.740(a) & (b);

(4) Certified Duplicate Copy of Items (1 through 3); and

(5) Associate Power of Attorney and Change of Correspondence Address.

Please charge all fees that are due or which become due in connection with the accompanying application for patent term extension to Deposit Account No. 02-1445. For accounting purposes, this transmittal letter is submitted in triplicate.

Respectfully Submitted,

SPRUNG HORN KRAMER AND WOODS

By _____
Kurt G. Briscoe
Reg. No. 33,141

660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: KLAUS GROHE ET AL.
(Patentee's name)

Patent No.: (number) 4,670,444

Issued: (date) June 2, 1987

For: (title) 7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

BOX PATENT EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

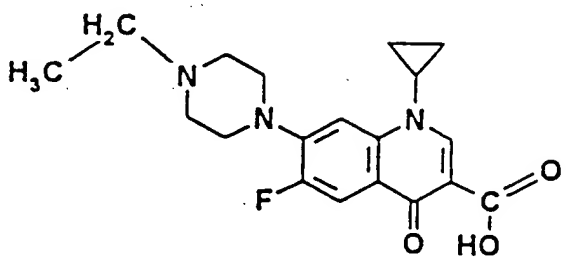
APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. § 156

Dear Sir:

Applicant, Bayer Aktiengesellschaft, a corporation of Germany, having a principal place of business at Leverkusen, Germany, is the assignee of the entire interest in and to Letters Patent of the United States No. 4,670,444, granted to Klaus Grohe, Hans-Joachim Zeiler, and Karl Metzger by virtue of an assignment of such patent to Bayer Aktiengesellschaft, recorded on Reel 4301, Frame 557. Applicant hereby submits this application for extension of patent term under 35 U.S.C. § 156, by providing the following information as required by 37 C.F.R. § 1.740:

(1) The approved product is BAYTRIL®, which contains the active ingredient Enrofloxacin, which has the chemical name 1-

cyclopropyl-7-(4-ethyl-1-piperazinyl)-6-fluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid, and has the following structure:



BAYTRIL® (Enrofloxacin) was previously approved on January 24, 1989, under Section 512 of the Federal Food, Drug and Cosmetic Act for commercial marketing or use for treating susceptible bacterial infections in dogs (NADA #140-441).

(2) The approved product was subject to regulatory review under the Federal Food, Drug, and Cosmetic Act, Section 512.

(3) BAYTRIL® received permission for commercial marketing or use under Section 512 of the Federal Food, Drug, and Cosmetic Act on October 4, 1996.

(4) This application for extension of patent term under 35 U.S.C. § 156 is being submitted within the sixty (60) day period permitted for submission, the last day for said submission being December 3, 1996.

(5) The complete identification of the patent for which an extension is being sought is as follows:

Inventors:	Klaus Grohe; Hans-Joachim Zeiler and Karl Metzger
Patent No.:	4,670,444
Issued:	June 2, 1987
Expiration Date:	December 9, 2003

(6) A copy of the patent for which an extension is being sought is attached herewith as "Attachment A."

(7) U.S. Patent No. 4,670,444 is subject to a terminal disclaimer and an amended terminal disclaimer, copies of which are attached hereto as "Attachment B" and "Attachment C", respectively. Also, one certificate of correction was issued in U.S. Patent No. 4,670,444. A copy of this certificate of correction is also attached as "Attachment D." Also, two maintenance fee payments have been made in connection with U.S. Patent No. 4,670,444. Copies of the maintenance fee payment receipts are attached as "Attachment E" and "Attachment F."

(8) U.S. Patent No. 4,670,444 claims the approved product, i.e., BAYTRIL®, as identified in paragraph (1) hereinabove, the active ingredient contained in BAYTRIL®, i.e., Enrofloxacin, as also identified in paragraph (1) hereinabove, a method of using the approved product for combating bacterial illnesses, and,

also, an animal feed, food concentrate or drinking water comprising the approved product. More specifically, the claims of U.S. Patent No. 4,670,444 read on the approved product, BAYTRIL®, or the active ingredient, Enrofloxacin, as follows:

Patent claim 1, which claims compounds per se, covers Enrofloxacin when A is CR^3; R^3 denotes a halogen atom, namely fluorine; Z is CH; and R^1 and R^2 together with the nitrogen atom and a further nitrogen atom form a six-membered ring, namely a piperazin-1-yl ring, which is substituted by alkyl, namely ethyl, at the 4-position of said ring.

Patent claim 2, which also claims compounds per se, also covers Enrofloxacin when A is CR^3 and R^3 is fluorine.

Patent claim 3, which also claims compounds per se, also covers Enrofloxacin when R^1 and R^2 together with the nitrogen atom and R^4-substituted nitrogen as a further heteroatom form a six-membered ring, namely 4-R^4-piperazin-1-yl, and R^4 is alkyl, namely ethyl.

Patent claim 5, which also claims compounds per se, also covers Enrofloxacin when R denotes ethyl.

Patent claim 14, which also claims compounds per se, claims Enrofloxacin specifically.

Patent claim 16 covers a pharmaceutical composition comprising an antibacterially effective amount of any compound of patent claim 1 in admixture with an inert pharmaceutical carrier.

Patent claim 1 covers Enrofloxacin as explained above. The approved product contains the active compound Enrofloxacin in admixture with benzyl alcohol, propylene glycol and purified water. The patent expressly identifies benzyl alcohol, propylene glycol and water as customary diluents and, therefore, inert pharmaceutical carriers. See U.S. Patent No. 4,670,444 at column 13, lines 29-31. Therefore, patent claim 16 covers BAYTRIL®.

Patent claim 18 covers the same pharmaceutical composition as claim 16, except that the active ingredient is required to be present in an amount of from 0.5% to 95% by weight. The approved product contains 3.23% by weight of Enrofloxacin. Therefore, patent claim 18 also covers BAYTRIL®.

Patent claim 21 covers a method of combating bacterial illnesses in warm-blooded animals which comprises administering to the animals an antibacterially effective amount of an active compound according to claim 1 either alone or in admixture with a diluent. Patent claim 1 covers Enrofloxacin as explained above. The approved product contains pharmaceutically acceptable diluents as also explained above. The approved product is approved for administration to turkeys and chickens, which are warm-blooded animals. The approved product contains Enrofloxacin in amount which is effective to combat bacteria in such turkeys and chickens, i.e., an antibacterially effective amount. Therefore, patent claim 21 covers the approved method of using BAYTRIL® to combat bacterial illnesses in turkeys and chickens.

Patent claim 22 covers an animal feed, food concentrate or drinking water comprising an active compound according to claim 1. Patent claim 1 covers Enrofloxacin as explained above. Moreover, the approved product is approved for use and intended to be used in the drinking water of turkeys and chickens. Therefore, patent claim 22 covers BAYTRIL® when added to drinking water.

(9) The relevant dates and information pursuant to 35 U.S.C. § 156 to enable the Secretary of Health and Human Services to determine the length of the applicable regulatory review period are as follows:

(a) U.S. Patent No. 4,670,444 was issued on Jun. 2, 1987;

(b) First application for investigational new drug exemption "INAD" for BAYTRIL® (Enrofloxacin) was filed on Nov. 20, 1984, INAD No. 4368; The second application for investigational new drug exemption "INAD" for BAYTRIL® (Enrofloxacin) was filed on Oct. 20, 1985, INAD No. 4586.

(c) New drug application ("NADA") for BAYTRIL® (Enrofloxacin) was submitted on Aug. 26, 1986, NADA No. 140-828;

(d) NADA 140-828 E-0018 for BAYTRIL® (Enrofloxacin) was approved on Oct. 4, 1996.

(10) A brief description of the activities undertaken by the Applicant during the applicable regulatory review period with respect to BAYTRIL® and the significant dates applicable to such activities is attached herewith as "Attachment G", and is a chronological synopsis of the major communications from Aug. 26, 1986 to Oct. 4, 1996 concerning 'testing ' and phases of 'approval'.

(11) Applicant is of the opinion that U.S. Patent No. 4,670,444 is eligible for extension under 35 U.S.C. § 156 because it satisfies the requirements for such extension as follows:

(a) 35 U.S.C. § 156(a)

U.S. Patent No. 4,670,444 claims the approved product, i.e., BAYTRIL®, as identified in paragraph (1) hereinabove, the active ingredient contained in BAYTRIL®, i.e., Enrofloxacin, as also identified in paragraph (1) hereinabove, a method of using the approved product for combating bacterial illnesses, and, also, an animal feed, food concentrate or drinking water comprising the approved product.

(b) 35 U.S.C. § 156(a)(1)

The term of U.S. Patent 4,670,444 has not expired before submission of this application for extension;

(c) 35 U.S.C. § 156(a)(2)

The term of U.S. Patent 4,670,444 has never been extended under 35 U.S.C. § 156(e)(1);

(d) 35 U.S.C. § 156(a)(3)

The application for extension is submitted by the agent of the owner of record of U.S. Patent 4,670,444 in accordance with the requirements of 35 U.S.C. § 156(d) and the guidelines of the U.S. Patent and Trademark Office;

(e) 35 U.S.C. § 156(a)(4)

The approved product, BAYTRIL®, has been subject to regulatory review period before its commercial marketing or use;

(f) 35 U.S.C. § 156(a)(5)(A)

The permission for the commercial marketing or use of the product, BAYTRIL®, after the regulatory review period is the first permitted commercial marketing or use of the product under the provision of the Federal Food, Drug, and Cosmetic Act, under which such regulatory review period occurred; and

(g) 35 U.S.C. § 156(c)(4)

No other patent has been extended for the same regulatory review period for the product, BAYTRIL®.

(h) 35 U.S.C. § 156(d)(1)

The application is submitted within the permitted 60 day period beginning on the date the product first received permission for commercial marketing or use.

The length of extension of the patent term of U.S. Patent No. 4,670,444 claimed by Applicant is five (5) years or 1827 days (two leap years, 2004 and 2008, are involved), the length of extension was determined pursuant to 35 U.S.C. § 156 as follows:

(a) The regulatory review period under 35 U.S.C. § 156(g)(4)(B) began 11/20/84 and ended 10/4/96, which is the sum

of 4336 days.

(b) The period of review, "Testing Period," under 35 U.S.C. § 156(g)(4)(B)(i) was from 11/20/84 (INAD submission date) until 8/26/86(NADA submission date), which is 644 days.

(c) The period of review, "Application Period," under 35 U.S.C. 156(g)(4)(B)(ii) was from 8/26/86(NADA submission date), until 10/4/96 (NADA approval date), which is 3692 days.

(d) The regulatory review period, 4336 days, upon which the period of extension is calculated is the entire regulatory review period as determined above, not to exceed five years under 35 U.S.C. § 156(g)(6)(A).

In compliance with 35 U.S.C. § 156(c)(3), the period remaining in the term of U.S. Patent No. 4,670,444, after NADA approval of BAYTRIL®, is from 10/4/96 (the NADA approval date) until 12/3/2003 (the original patent expiration date), which is 2615 days, which when added to the five-year period of extension claimed by applicant of 1827 days is 4442 days, or approximately 12.2 years, and therefore is not in excess of fourteen (14) years.

Therefore, the length of extension of patent term claimed by applicant is five (5) years or 1827 days (two leap years, 2004 and 2008, are involved).

(12) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determination to be made relative to this application for extension.

(13) The prescribed fee for receiving and acting upon this application for extension is to be charged to Applicant's Deposit Account No. 02-1445 as authorized in the accompanying letter, which is submitted in duplicate.

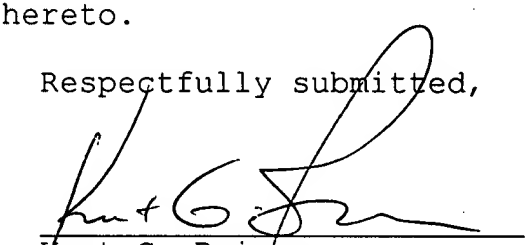
(14) Inquiries and/or other correspondence relating to this application for patent term extension are to be directed to:

Kurt G. Briscoe
SPRUNG HORN KRAMER & WOODS
660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

(15) A certified duplicate copy of the application papers is submitted herewith.

(16) The requisite Declaration, set forth in §§ 1.740 (a)(17) and (b) is also attached hereto.

Respectfully submitted,



Kurt G. Briscoe
Registration No. 33,141
SPRUNG HORN KRAMER & WOODS
660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

Dated: December 3, 1996

EXPRESS MAIL CERTIFICATE

It is hereby certified that the following items:

(1) Letter of Transmittal of Application for Extension of Patent Term Under 35 U.S.C. § 156;

(2) Application for Extension of Patent Term Under 35 U.S.C. § 156;

(3) Attachments A through G thereto;

(4) Declaration Pursuant to 37 C.F.R. § 1.740(a) & (b);

(5) Certified Duplicate Copy of Items (2) through (4); and

(6) Associate Power of Attorney and Change of Correspondence Address;

are being deposited with the United States Postal Services "Express Mail Post Office to Addressee" service under 37 C.F.R. § 1.10 in an envelope bearing "Express Mail" mailing label number EI001520016US and addressed to BOX PATENT EXTENSION, Commissioner of Patents and Trademarks, Washington, D.C. 20231, on the date indicated below:

Date: December 3, 1996 By: Adele Benitez
Adele Benitez

Bayer S844-JG1
Le A 21 353

United States Patent [19]

Grohe et al.

[11] **Patent Number: 4,670,444**

[45] **Date of Patent: Jun. 2, 1987**

[54] **7-AMINO-1-CYCLOPROPYL-4-OXO-1, 4-DIHYDRO-QUINOLINE-AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS**

[75] Inventors: **Klaus Grohe**, Odenthal; **Hans-Joachim Zeiler**, Velbert; **Karl G. Metzger**, Wuppertal, all of Fed. Rep. of Germany

[73] Assignee: **Bayer Aktiengesellschaft**, Leverkusen, Fed. Rep. of Germany

[21] Appl. No.: **614,923**

[22] Filed: **May 29, 1984**

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 292,560, Aug. 13, 1981, abandoned, and a continuation-in-part of Ser. No. 436,112, Oct. 22, 1982, abandoned. ~~420~~ 2052

[30] **Foreign Application Priority Data**

Sep. 3, 1980 [DE] Fed. Rep. of Germany 3033157
Oct. 29, 1981 [DE] Fed. Rep. of Germany 3142854

[51] **Int. Cl.**[4] **A61K 31/495**; C07D 521/00

[52] **U.S. Cl.** **514/300**; 514/236; 514/254; 514/312; 544/127; 544/128; 544/295; 544/362; 544/363; 546/123; 546/156

[58] **Field of Search** 544/362, 363, 295, 127, 544/128; 424/250; 546/156, 123; 514/254, 312, 300, 236

[56] **References Cited**

U.S. PATENT DOCUMENTS

3,849,421	11/1974	Nagagome et al.	546/156
4,146,719	3/1979	Irikura	544/363
4,284,629	8/1981	Grohe et al.	544/279
4,292,317	9/1981	Pesson	544/363
4,472,579	9/1984	Irikura et al.	544/363
4,522,819	6/1985	Fox, Jr. et al.	544/363
4,556,709	12/1985	Grohe et al.	544/279

FOREIGN PATENT DOCUMENTS

0009425	4/1980	European Pat. Off.	544/363
2939786	4/1980	Fed. Rep. of Germany	544/363

OTHER PUBLICATIONS

Arzneimittelchemie I pp. 32–33, Georg Thieme Verlag Stuttgart, 1976.

Primary Examiner—Glennon H. Hollrah
Assistant Examiner—James H. Turnipseed
Attorney, Agent, or Firm—Sprung Horn Kramer & Woods

[57] **ABSTRACT**

The invention relates to 7-amino-1-cyclo-propyl-4-oxo-1, 4-dihydro-naphthyridine (or quinoline)-3-carboxylic acids of Formula I as defined in the specification. Also included in the invention is a process for the preparation of said compounds of Formula I and Ia. Further, the invention includes compositions containing the compounds of Formula I or Ia and the use of said compounds and compositions as antibacterial agents.

22 Claims, No Drawings

ATTACHMENT "A"

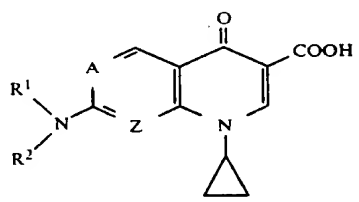
7-AMINO-1-CYCLOPROPYL-4-OXO-1, 4-DIHYDRO-QUINOLINE-AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

This application is a continuation-in-part of our application Ser. No. 292,560 filed Aug. 13, 1981, now abandoned and a continuation-in-part of our application Ser. No. 436,112 filed Oct. 22, 1982 now abandoned.

The present invention relates to certain new 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline- and naphthyridine-3-carboxylic acid compounds, to processes for their production, to their use as antibacterial agents, and to feed additives containing these compounds.

It has already been disclosed that 7-amino-1-ethyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acids have antibacterial properties [see Eur. J. Med. Chem. 12, 541–547 (1977)]; and it has also been disclosed that 1-ethyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acids possess antibacterial properties [J. Med. Chem. 23, 1358 (1980)].

According to the present invention there are provided compounds which are 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline- and naphthyridine-3-carboxylic acids of the formula



(I)

or a salt thereof,

in which A represents a nitrogen atom or CR^3,

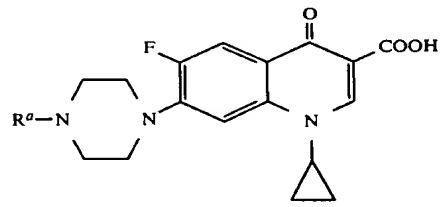
wherein R^3 denotes a hydrogen, a nitro group or a halogen atom (preferably a fluorine or chlorine atom), or a nitrile, carboxamide, carboxyl or ester group, and Z represents a nitrogen atom or C—H, and A and Z cannot simultaneously be nitrogen atoms, and R^1 and R^2 are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl or alkinyl radical which has up to 12 (preferably up to 6) carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in each alkyl radical, nitrile, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, aryl and hetaryl, or furthermore represent a cycloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substitute and, if appropriate, a further hetero-atom (such as oxygen or sulphur, or NR^4) form a 3-membered to 7-membered ring which can be monosubstituted disubstituted or polysubstituted by radical(s) selected from alkyl or alkenyl with up to 6 carbon atoms, hydroxyl, alkoxy or alkyl-mercapto with 1 to 3 carbon atoms, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, nitrile group and aryl, and which can furthermore possess a double bond, and R^4 represents a hydrogen atom, or a branched or straight-chain alkyl, alkenyl or alkinyl group which has up to 6 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms per alkyl radical, and alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, or represents an aralkyl group which is optionally substituted in the aryl radical by C_1–C_2-alkyl, halogen, preferably chlorine, NO_2 and/or NH_2 and has up to 4 (preferably 1 2) carbon atoms in the aliphatic part, or an optionally substituted phenyl or naphthyl group or a heterocyclic radical (such as a radical of pyridine, pyrimidine, thiazole or benzothiazole), or R^4 denotes an alkoxycarbonyl group which is optionally substituted by an aryl radical and has 1 to 4 carbon atoms in the alcohol part, an alkanoyl radical with 1 to 6 carbon atoms, an aryl radical, an optionally substituted C_1–C_3-alkyl- or aryl-(thio) carbamoyl radical, an C_1–C_3-alkyl- or aryl-sulphonyl radical or an optionally substituted aminosulphonyl radical.

As used herein and unless otherwise specified, the term "aryl" is preferably mono- or bi-cyclic carbocyclic aryl, such as phenyl or naphthyl; the term "aralkyl" is preferably mono- or bi-cyclic carboxylic aryl-C_1–C_4-alkyl, such as benzyl, phenethyl, naphthyl-methyl and naphthyl-ethyl; the term "hetaryl" is preferably mono- or bi-cyclic, N-, O- or S-heteroaryl, such as pyridine, thiophene and furane; and the term "aroyl" is preferably benzoyl or naphtyoyl.

The compounds of the present invention have a superior antibacterial action against both gram positive and gram negative bacteria, including *pseudomonas aerwginosa*, to that of the known quinolone- and azaquinolone-carboxylic acids.

The abovementioned aryl radicals, preferably the phenyl or naphthyl radical, are optionally monosubstituted di-substituted or polysubstituted by substituent(s) selected from halogen (preferably fluorine, chlorine and/or bromine), alkyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, aryloxy or arylmercapto, trifluoromethyl, nitro, nitrile and a carboxylic and ester group with 1 to 4 carbon atoms in the alcohol part.

Further according to the present invention and within the scope of the compounds identified above under Formula (I) there are now provided, as new compounds, 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperzino-quinoline-3-carboxylic acids of the general formula



(I')

or salts thereof,

in which, R^a denotes a hydrogen atom or a methyl, ethyl or β-hydroxyethyl group.

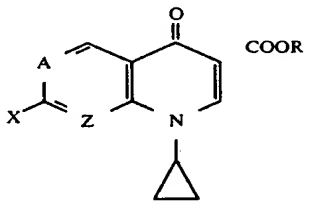
Suitable salts are those of inorganic or organic acids, p.e. hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphonic acid, acetic acid, succinic acid, malic acid etc. Suitable salts are furthermore those of anorganic or organic bases, p.e. KOH, NaOH,

$Ca(OH)_2$,$Al(OH)_3$, piperidine, morpholine, ethylamine, triethylamine etc.

The compounds of the formula (I') may contain various amounts of water.

According to the present invention, there is further provided a process for the production of a compound of the present invention characterized in that

(a) a quinolone-carboxylic acid of the formula



(II)

in which

R denotes a hydrogen atom,

A and Z have the abovementioned meaning and

X represents a halogen atom or an alkylsulphonyl group with 1 to 4 carbon atoms,

is reacted with an amine of the formula

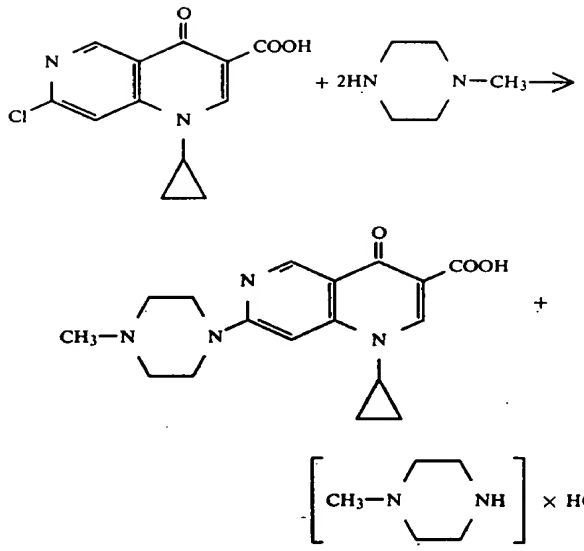
(III)

in which

R^1 and R^2 have the abovementioned meanings or

(b) a 7-halogeno-naphthyridine-3-carboxylic acid ester of a compound of formula (II), as given above, in which R denotes an alkyl radical and A, Z and X have the abovementioned meanings, is reacted with an amine of formula (II), as defined above, if appropriate in the presence of an acid-binding agent, (such as triethylamine or pyridine) and then the resulting 7-amino-naphthyridine-3-carboxylic acid ester is hydrolyzed under alkaline conditions.

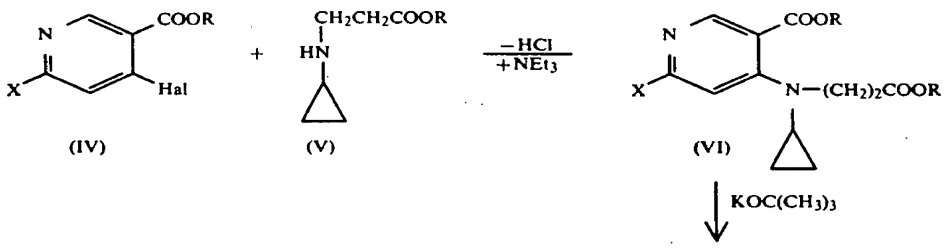
If, for example, 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and N-methylpiperazine are used as reactants in the reaction, the course of the reaction variant (a) according to the present invention is illustrated by the following equation:



The starting compound of formula (II) can be prepared in the following manner (in which the formulae for the compounds concerned are given in the following reaction scheme):

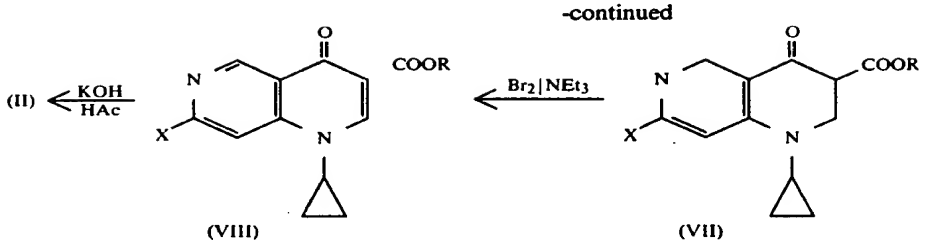
The starting substance used is, for example, a 4-halogeno-pyridine-3-carboxylic acid ester of the formula (IV), which is substituted by a radical X in the 6-position, this ester is largely converted selectively into a monosubstitution product of the formula (IV), the halogen atom in the 4-position being replaced by the amine radical, with a β-cyclopropylamino-propionic acid ester of the formula (V), preferably a methyl or ethyl ester, which is readily accessible by reaction of corresponding acrylic acid ester with cyclopropylamine. The monosubstitution product of the formula (VI) is converted into a tetrahydro-naphthyridine-3-carboxylic acid ester of the formula (VII) by Dieckmann cyclisation in the presence of a strong base (such as potassium t-butylate or sodium hydride). The carboxylic acid ester of the formula (VIII) is obtained from the ester of formula (VII) with bromine or sulphuryl chloride and triethylamine or pyridine as the dehydrohalogenating agent, and the compound of the formula (VIII) is saponified with an alkali to give the carboxylic acids of the formula (II) (in which R represents a hydrogen atom, A represents a nitrogen atom and Z represents CH).

One version of the abovementioned process for the production of a starting substance of formula (II) is represented by the reaction scheme:



(IV) (V) (VI)

-continued



(VIII) (VII)

Preferred possible diluents for the reaction variant (a) or (b) are ethanol, dioxane, toluene, dimethylformamide and dimethylsulphoxide.

Acid-binding agents which can be used in reaction variant (b) are, preferably, alkali carbonates, alkali metal hydroxides or tert.-organic bases (such as, preferably, triethylamine and pyridine).

The reaction temperatures for reaction variants (a) or (b) can be varied within a substantial range. In general, the reaction is carried out at a temperature between 20° and 180° C., preferably between 60° and 140° C.

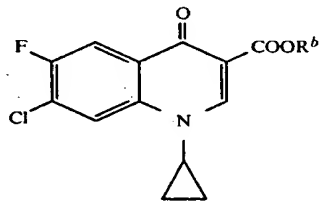
Both reaction variants can be carried out under normal pressure, but also under increased pressure, especially in the case of gaseous and low-boiling amines of the formula (III). In general, the reaction is carried out under pressures between 1 and 100 bars, preferably between 1 and 10 bars.

In carrying out reaction variant (a) or (b), 1 to 5 moles of amine, preferably 2 to 3 moles of amine, are employed per mole of carboxylic acid.

The 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid used as a starting material can be prepared in a multi-stage reaction sequence, for example starting from 4,6-dichloro-nicotinic acid ethyl ester, which is known (see Recueil Trav. chim. Pays-bas. 69, 687 (1950). The methyl ester is known from U.S. Pat. Nos. 4,066,645 and 4,075,210.

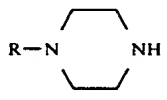
According to the present invention there is further provided a process for the production of a compound of the invention of Formula (I') in which

(a') 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid of the formula



(II')

in which R^b denotes a hydrogen atom, is reacted with piperazine or a piperazine derivative of the formula



(III')

in which

R^a has the meaning given above, or

(b') a compound of the formula (II'), as given in reaction variant (a) in which R^b denotes an alkyl group, is reacted with a compound of formula (III') as defined in reaction variant (a), if appropriate, in the presence of an acid-binding agent (such as triethylamine, 1,4-diazabicyclo[2,2,2]octane or 1,8-diaza-bicyclo[5,4,0]undec-7-ene) and the 7-piperazino-quinolone-3-carboxylic acid ester obtained is hydrolysed under alkaline conditions to give a compound of formula (I'),

and the compound of formula (I') obtained by reaction variant (a) or (b) is converted, if desired, into a salt and/or a hydrate thereof.

The reaction variant (a) is preferably carried out in a diluent (such as dimethylsulphoxide, N,N-dimethylformamide, hexamethyl-phosphoric acid trisamide, sulpholane, water, an alcohol or pyridine) and at a temperature between 20° and 200° C., preferably between 80° and 180° C.

The reaction variants can be carried out under normal pressure, but also under elevated pressure, in particular in the case of a low-boiling solvent. In general, the reaction is carried out under pressures between about 1 and about 100 bar, preferably between 1 and 10 bar.

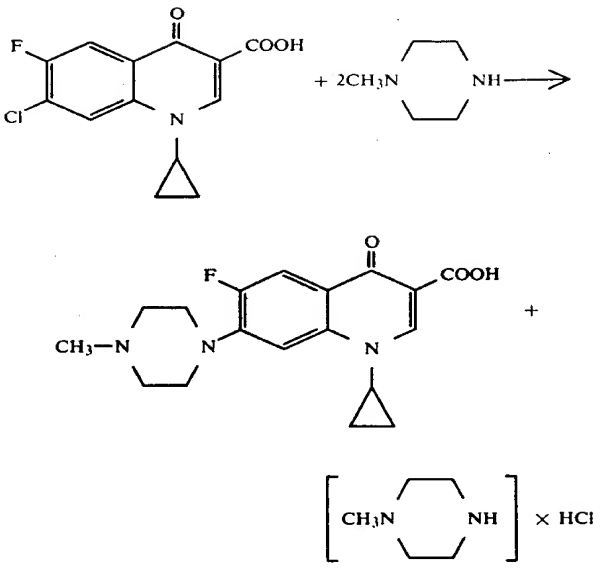
In carrying out reaction variants 1 to 5 mol of alkylpiperazine (in the case of piperazine 1 to 15 mol), preferably 2 to 3 mol of alkylpiperazine (in the case of piperazine 5 to 10 mol), are employed per mol of carboxylic acid, or carboxylic acid ester of formula (II').

Among the new 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazo-quinoline-3-carboxylic acid salts and hydrates of the invention those salts or hydrates that are pharmaceutically acceptable are particularly important and are preferred.

The new free 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acids of the general formula (I) and their salts and hydrates can be interconverted in any suitable manner; methods for such interconversion are known in the art.

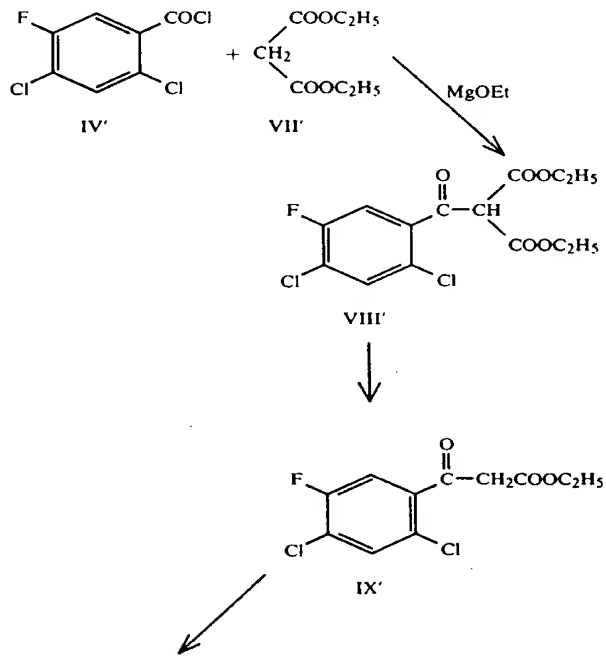
Thus the 7-piperazino-quinolone-3-carboxylic acids of formula (I) obtained can, if required, be converted into a salt using an organic or inorganic acid. Examples of acids which are suitable for salt formation are hydrohalic acids, such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulphuric acid, acetic acid, citric acid and benzenesulphonic acid.

If 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and methylpiperazine are used as starting materials in reaction variant (a), the course of the reaction is illustrated by the following equation:



The following may be mentioned individually as active compounds according to the present invention: 7-piperazino-, 7-(4methylpiperazino)-, 7-(4-ethylpiperazino)-, 7-(4-β-hydroxyethylpiperazino)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and pharmaceutically tolerated acid addition salts or alkali metal alkaline earth metal or ammonium salts of these compounds.

The starting compounds of formula (II') can be prepared via a malonic ester synthesis, according to the following equation:



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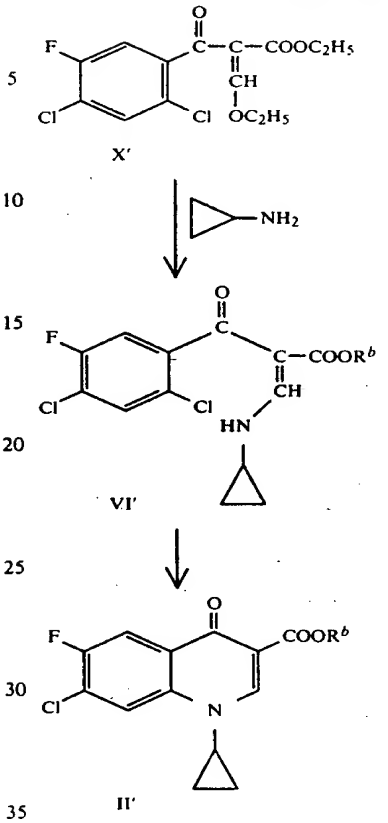


According to this equation, diethyl malonate of formula (VII) is acylated with a compound of formula (IV') in the presence of magnesium alcoholate to give the acylmalonate of formula (VIII (Organicum, 3rd edition 1964, page 438).

The ethyl aroylacetate of formula (IX') is obtained in good yield by partial hydrolysis and decarboxylation of the compound of formula (VIII') in an aqueous medium containing a catalytic amount of p-toluenesulphonic acid, and is converted with triethyl o-formate/acetic anhydride into the ethyl 2-(2,4-dichloro-5-fluoro-benzoyl)-3-ethoxyacrylate of formula (X'). The reaction of the compound of formula (X') with cyclopropylamine in a solvent (such as methylene chloride, alcohol, chloroform, cyclohexane or toluene) leads to the desired intermediate product of formula (VI) in a slightly exothermic reaction.

The cyclisation reactin VI→II (R^1=alkyl) is carried out in a temperature range of 60° to 280° C., preferably 80° to 180° C.

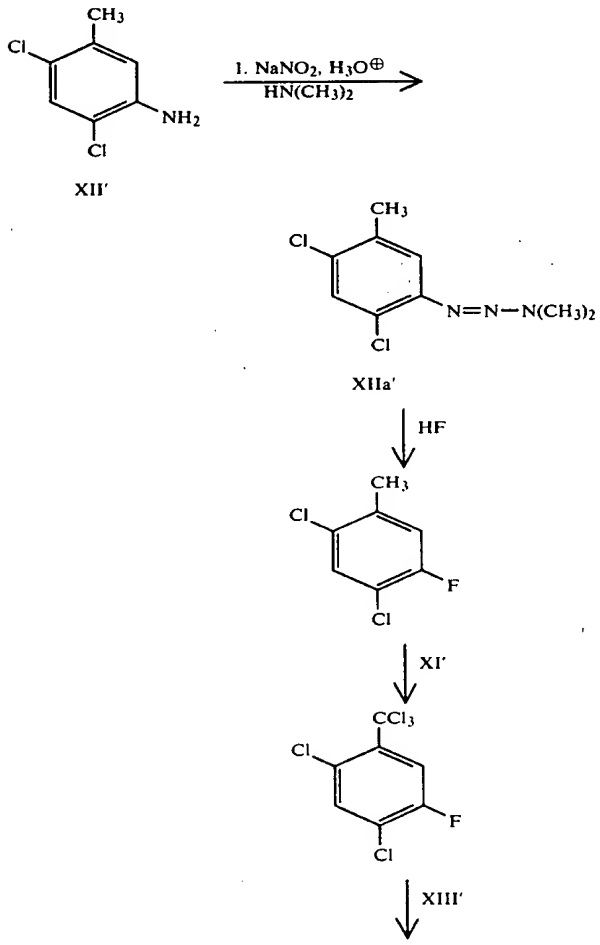
Dioxane, dimethylsulphoxide, N-methyl-pyrrolidone, sulpholane, hexamethylphosphoric acid triamide and preferably N,N-dimethylformamide can be used as diluents.

Potassium t-butanolate, butyl-lithium, lithium-phenyl, phenyl magnesium bromide, sodium ethylate and particularly preferably sodium hydride or potassium carbonate are suitable acid-binding agents for this reaction stage. It can be advantageous to employ an excess of 10 mol% of base.

The 2,4-dichloro-5-dichloro-5-fluoro-benzoyl chloride of formula (IV) used as a starting material for this

synthesis route, the corresponding carboxylic acid, and the 3-fluoro-4,6-dichlorotoluene of formula (XI) required for the preparation of formula (IV) were not yet known in the literature and form a further subject of the present invention.

The equation below shows the preparation of these precursors or intermediate products, starting from 2,4-dichloro-5-methyl-aniline of formula (XIII).



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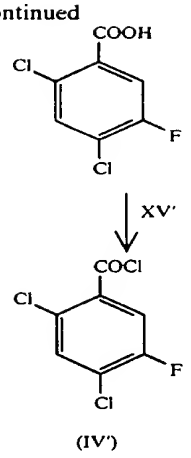


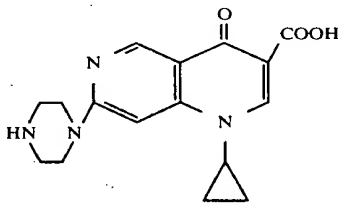
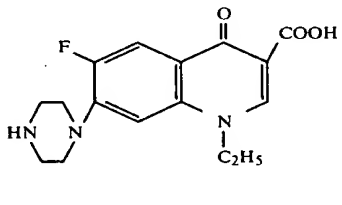
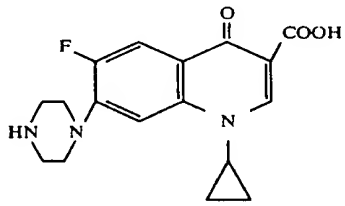
According to this equation, 2,4-dichloro-5-methyl-aniline of formula (XII') is diazotised by means of $NaNO_2$, and the resulting diazonium salt is converted into the triazene of formula (XIIa'), using dimethylamine.

Triazene of formula (XIIa') is dissolved in excess anhydrous HF. In this step, the triazene is cleaved to give 2,4-dichloro-5-methyl:diazonium fluoride and dimethylamine. Without intermediate isolation, this solution is cleaved thermally at 130° to 140° to give 3-fluoro-4,6-dichlorotoluene XI', N_2being split off (Yield: 77.7% of theory).

The 3-fluoro-4,6-dichlorotoluene of formula (XI') is chlorinated in a temperature range from 110° to 160° C., under UV irradiation, to give 2,4-dichloro-5-fluoro-1-trichloro-methylbenzene of formula (XIII').

The hydrolysis of the compound of formula (XIII') with 95 percent sulphuric acid leads to 2,4-dichloro-5-fluoro-benzoic acid of formula (XV'), which is converted with thionyl chloride into the carboxylic acid-chloride of formula (IV').

The compounds according to the invention are distinguished by a particularly good antibacterial action against gram positive and gram negative bacteria, in particular in comparison with the compounds of German Patent Application No. P 30 33 157.8 of 3.9.1980 and DE-OS (German Published Specification) No. 2,804,097, as can be seen from the table below.

	 Example 2 of German Patent Application P 30 33 157.8 of 3.9.80	 (disclosed in DE-OS (German Published Specification) 2,804,097)	 (compound according to the invention, of the formula I (R = H)
Staphylococcus aureus 133	8	1	0.25–0.5
E. coli A 261	1	0.125	0.06
E. coli Neum.	1	0.25	0.06
Klebsiella	1	0.25	0.06

-continued

8085 Proteus 1017	0.5	0.06	0.03
Pseudomonas aeruginasa W	4	1	0.5

Agar dilution test
DST (dexhase sensitivity test) medium: 1-2 × 10^3 germs/plate

New antibacterial active compounds which may be mentioned specifically are: 7-methylamino-, 7-benzylamino-, 7-pyrrolidino-, 7-morpholino-; 7-piperidino-, 7-piperazino-, 7-(4-methylpiperazino)-, 7-(4-benzylpiperazino)-, 7-(4-β-hydroxyethylpiperazino)-, 7-(4-γ-hydroxypropyl-piperazino)-, 7-(4-formylpiperazino)- or 7-(4-hydroxypiperidino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and pharmaceutically acceptable acid addition salts or alkali or alkaline earth metal salts of these compounds.

It has furthermore been found that the compounds according to the invention have outstanding antimicrobial properties.

In particular, they have a broad bacteriostatic and bactericidal action against Gram-positive bacteria, such as Staphylococci and Streptococci, and Gram-negative bacteria, such as Escherichia, Proteus, Providencia, Enterobacter, Klebsiella, Salmonella and Pseudomonas. The list of sensitive bacteria is to be regarded as a list of examples and in no way restrictive.

The improved broad antibacterial activity of the compounds according to the invention enable them to be used as active compounds both in medicine, in which they can be used both for preventing and for the treatment of systemic or local bacterial infections, in particular of the urinary tract. The compounds according to the invention can furthermore also be used as feed additives for promoting growth and for improving feed utilisation in livestock husbandry, in particular in the rearing of animals for fattening. The active compounds are then preferably administered via the feed and/or the drinking water.

The present invention furthermore relates to agents which contain the new compounds according to the invention. These agents include, for example, feed concentrates, for livestock husbandry, which can also contain, as is customary, vitamins and/or mineral salts, in addition to the active compounds, and pharmaceutical formulations.

Among the new 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid salts of the invention, those salts that are pharmaceutically acceptable are particularly important and are preferred, alkali metal salts and alkaline earth metal salts being particularly preferred.

The new free 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-carboxylic acids of the general formula (I) and (I') and their salts can be interconverted in any suitable manner; methods for such interconversion are known in the art.

As stated above, the invention also relates to the use in medicine of the compounds of the invention.

The present invention provides a pharmaceutical composition containing as active ingredient a compound of the invention in admixture with an inert pharmaceutical carrier, e.g. a solid or liquefied gaseous diluent, or in admixture with a liquid diluent other than a solvent of a molecular weight less than 200 (preferably less than 350) except in the presence of a surface active agent.

The invention further provides a pharmaceutical composition containing as active ingredient a compound of the invention in the form of a sterile and/or physiologically isotonic aqueous solution.

The invention also provides a medicament in dosage unit form comprising a compound of the invention.

The invention also provides a medicament in the form of tablets (including lozenges and granules), dragees, capsules, pills, ampoules or suppositories comprising a compound of the invention.

"Medicament" as used in this Specification means physically discrete coherent portions suitable for medical administration. "Medicament in dosage unit form" as used in this Specification means physically discrete coherent units suitable for medical administration each containing a daily dose or a multiple (up to four times) or submultiple (down to a fortieth) of a daily dose of the compound of the invention in association with a carrier and/or enclosed within an envelope. Whether the medicament contains a daily dose or, for example, a half, a third or a quarter of a daily dose will depend on whether the medicament is to be administered once or, for example, twice, three times or four times a day respectively.

The pharmaceutical composition according to the invention may, for example, take the form of ointments, gels, pastes, creams, sprays (including aerosols), lotions, suspensions, solutions and emulsions of the active ingredient in aqueous or non-aqueous diluents, syrups, granulates or powders.

The diluents to be used in pharmaceutical compositions (e.g. granulates) adapted to be formed into tablets, dragees, capsules and pills include the following: (a) fillers and extenders, e.g. starch, sugars, mannitol, and silicic acid; (b) binding agents, e.g. carboxymethyl cellulose and other cellulose derivatives, alginates, gelatine and polyvinyl pyrrolidone; (c) moisturizing agents, e.g. glycerol; (d) disintegrating agents, e.g. agar-agar, calcium carbonate and sodium bicarbonate; (e) agents for retarding dissolution e.g. paraffin; (f) resorption accelerators, e.g. quaternary ammonium compounds; (g) surface active agents, e.g. cetyl alcohol, glycerol monostearate; (h) adsorptive carriers, e.g. kaolin and bentonite; (i) lubricants, e.g. talc, calcium and magnesium stearate and solid polyethyl glycols.

The tablets, dragees, capsules and pills formed from the pharmaceutical compositions of the invention can have the customary coatings, envelopes and protective matrices, which may contain opacifiers. They can be so constituted that they release the active ingredient only or preferably in a particlar part of the intestinal tract, possibly over a period of time. The coatings, envelopes and protective matrices may be made, for example, of polymeric substances or waxes.

The ingredient can also be made up in microencapsulated form together with one or several of the above-mentioned diluents.

The diluents to be used in pharmaceutical compositions adapted to be formed into suppositories can, for example, be the usual water-soluble diluents, such as polyethylene glycols and fats (e.g. cocoa oil and high esters (e.g. C_{14}-alcohol with C_{16}-fatty acid)) or mixtures of these diluents.

The pharmaceutical compositions which are ointments, pastes, creams and gels can, for example, contain the usual diluents, e.g. animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide or mixtures of these substances.

The pharmaceutical compositions which are powders and sprays can, for example, contain the usual diluents, e.g. lactose, talc, silicic acid, aluminium hydroxide, calcium silicate, and polyamide powder or mixtures of these substances. Aerosol sprays can, for example, contain the usual propellants, e.g. chlorofluorohydrocarbons.

The pharmaceutical compositions which are solutions and emulsions can, for example, contain the customary diluents (with, of course, the above-mentioned exclusion of solvents having a molecular weight below 200 except in the presence of a surface-active agent), such as solvents, dissolving agents and emulsifiers; specific examples of such diluents are water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils (for example ground nut oil), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbital or mixtures thereof.

For parenteral administration, solutions and emulsions should be sterile, and, if appropriate, blood-isotonic.

The pharmaceutical compositions which are suspensions can contain the usual diluents, such as liquid diluents, e.g. water, ethyl alcohol, propylene glycol, surface-active agents (e.g. ethoxylated isostearyl alcohols, polyoxyethylene sorbite and sorbitane esters), microcrystalline cellulose, aluminium metahydroxide, bentonite, agar-agar and tragacanth or mixtures thereof.

All the pharmaceutical compositions according to the invention can also contain colouring agents and preservatives as well as perfumes and flavouring additions (e.g. peppermint oil and eucalyptus oil) and sweetening agents (e.g. saccharin).

The pharmaceutical compositions according to the invention generally contain from 0.1 to 99.5% usually from 0.5 to 95% of the active ingredient by weight of the total composition.

In addition to a compound of the invention, the pharmaceutical compositions and medicaments according to the invention can also contain other pharmaceutically active compounds. They may also contain a plurality of compounds of the invention.

Any diluent in the medicaments of the present invention may be any of those mentioned above in relation to the pharmaceutical compositions of the present invention. Such medicaments may include solvents of molecular weight less than 200 as sole diluent.

The discrete coherent portions constituting the medicament according to the invention will generally be adapted by virtue of their shape or packaging for medical administration and may be, for example, any of the following: tablets (including lozenges and granulates), pills, dragees, capsules, suppositories and ampoules. Some of these forms may be made up for delayed release of the active ingredient. Some, such as capsules, include a protective envelope which renders the portions of the medicament physically discrete and coherent.

The production of the above-mentioned pharmaceutical compositions and medicaments is carried out by any method known in the art, for example, by mixing the active ingredient(s) with the diluent(s) to form a pharmaceutical composition (e.g. a granulate) and then forming the composition into the medicament (e.g. tablets).

This invention further provides a method of combating the above-mentioned diseases in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

The provision of new bactericides for combating bacteria which are resistant to known bactericides as is the case with compounds of the present invention is an enrichment of the state of the art.

The following examples illustrated but do not limit the invention.

EXAMPLE 1

7-(4-Methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (a compound of formula (I) in which R^1R^2N=4-methylpiperazino, A=N and B=CH).

A suspension of 2.64 g of 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid and 2.5 g of N-methylpiperazine in 30 ml of ethanol or DMSO (=Dimethylsulfoxide) was heated to the boiling point under reflux for 16 hours or to 135°-140° C. for two hours. The diluent was distilled off in vacuo, the residue was dissolved in 30 ml of 1N NaOH, the solution was filtered and the filtrate was acidified with 10 strength hydrochloric acid. The precipitate was filtered off and washed with water and ethanol. It could be recrystallised from N-dimethylformamide/ethanol. 3.1 g (94% of the theoretical yield) of 7-(4-methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid of melting point 326° C. (hydrochloride) (decomposition) were obtained.

EXAMPLES 2 TO 10

The carboxylic acids of Examples 2 to 19 were obtained by a procedure analogous to that in Example 1. They are summarised in Table 1. The labelling of the radicals R^1 and R^2 relates to the formula (I) of the description.

TABLE 1

Example No.	A	B	R^1 R^2	Decomposition Point (°C.)
2	N	CH	H $-(CH_2)_2N(CH_2)_2-$	322 (hydrochloride)
3	N	CH	$-(CH_2)_2O(CH_2)_2-$	286
4	N	CH	$-(CH_2)_2CH_2(CH_2)_2-$	297
5	N	CH	$-CH_2CH_2CH_2CH_2-$	330
6	N	CH	$-(CH_2)_2N(CH_2)_2-$ $\lvert$ CH_2CH_2OH	305 (hydrochloride)

TABLE 1-continued

Example No.	A	B	R^1 R^2	Decomposition Point (°C.)
7	N	CH	$-(CH_2)_2N(CH_2)_2-$ $(CH_2)_3OH$	(hydrochloride)
8	N	CH	$-(CH_2)_2N(CH_2)_2-$ CHO	300
9	N	CH	$-CH_2-CH-(CH_2)_3-$ OH	302
10	N	CH	$-(CH_2)_2CH(CH_2)_2-$ OH	279
1	CF	CH	H $-(CH_2)_2N(CH_2)_2-$	256 306 (hydrochloride)
2	CH	N	$-(CH_2)_2N(CH_2)_2-$ CH_3	279
3	CH	N	$-(CH_2)_2N(CH_2)_2-$ H	277
4	CF	CH	$-(CH_2)_2N(CH_2)_2-$ CH_3	249
5	CF	CH	$-(CH_2)_4-$	323
6	C—CN	N	H $-(CH_2)_2N(CH_2)_2-$	335 (hydrochloride)
7	C—CN	N	$-(CH_2)_2N(CH_2)_2-$ CH_3	295 (hydrochloride)
8	C—CN	N	$-(CH_2)_4-$	290
9	CF	CH	$-(CH_2)_2N(CH_2)_2-$ C_2H_5	306 (hydroiodide)

EXAMPLE 20

Preparation of precursors

(a) 6-Chloro-4-(N-2-methoxycarbonylethyl-N-cyclopropyl)-amino-pyridine-3-carboxylic acid methyl ester (a compound of formula (VI) in which R=methyl and X=chlorine).

A mixture of 28.6 g of β-cyclopropylamino-propionic acid methyl ester and 21 g of triethylamine was rapidly added dropwise to a solution of 41.2 g of 4,6-dichloropyridine-3-carboxylic acid methyl ester in 150 ml of toluene at 10° to 20° C., whilst cooling with ice and stirring. The ice-bath was removed and the mixture was stirred at room temperature for ½ hour and heated to the boiling point under reflux for 6 hours. The resulting suspension was washed with water and dried with Na_2SO_4 and the solvent was distilled off in vacuo. 59 g of the title compound were obtained as a brown oil.

(b) The β-cyclopropylaminopropionic acid methyl ester

This compound, used as a reactant in Example 20(a), was prepared as follows:

86 g of freshly distilled methyl acrylate which had been cooled to −60° C. was added dropwise to a solution, which had been cooled to −60° C. to −70° C., of 57 g of cyclopropylamine in 150 ml of ethanol in the course of about 3 hours. The mixture was then allowed to rise slowly to room temperature overnight, the solvent was distilled off in vacuo and the residue was then fractionated. 95 g of β-cyclopropylamino-propionic acid methyl ester passed over at 84°–86° C./22 mm Hg.

(c) 7-Chloro-1-cyclopropyl-4-oxo-1,2,3,4-tetrahydro-1,6-naphthyridine-3-carboxylic acid methyl ester (a compound of formula (VII) in which R=methyl and X=chlorine).

59 g of crude 6-chloro-4-(N-2-methoxycarbonylethyl-N-cyclopropyl)-amino-pyridine-3-carboxylic acid methyl ester were dissolved in 240 ml of anhydrous toluene, and 23 g of potassium t-butylate were rapidly added, whilst stirring. The mixture was left to stand overnight, 20 g of glacial acetic acid and 100 ml of water were added, the phases were separated, the toluene solution was washed again with water and dried with Na_2SO_4 and the toluene was stripped off in vacuo. After recrystallisation from methanol, 18 g of the carboxylic acid ester of melting point 155° to 157° C. were obtained.

(d) 7-Chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid methyl ester (a compound of formula (VIII) in which R=methyl and X=chlorine).

9.8 g of the tetrahydronaphthyridine-3-carboxylic acid methyl ester prepared according to Example 20(c) were dissolved in 200 ml of methylene chloride, and a solution of 5.9 g of bromine in 40 ml of CH_2Cl_2 was rapidly added dropwise at 10° to 15° C., whilst cooling with ice. The mixture is then stirred at ~10° C. for a further 10 minutes, 8 g of triethylamine were added and the ice-bath was removed. The mixture was subsequently stirred for 3 hours, washed twice with water and dried with Na_2SO_4, the solvent was distilled off in vacuo and the residue was recrystallised from dimethylformamide/ethanol. 8.8 g of 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid methyl ester of melting point 272° to 274° C. (decomposition) were obtained.

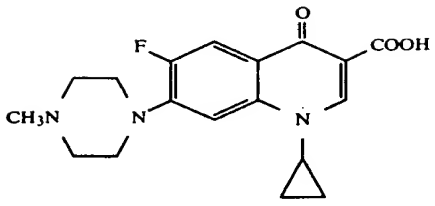
(e) 7-Chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid (a compound of formula (II) in which R=H, A=N, Z=CH and X=chlorine).

A solution of 5.7 g of potassium hydroxide in 300 ml of water was added to 27.85 g of the ester prepared according to Example 11(d). The mixture was heated to 85° to 95° C. for 30 minutes, whilst stirring, and the resulting solution was filtered at room temperature and acidified with glacial acetic acid. The precipitate was filtered off, washed with water and dried over calcium chloride in a vacuum drying cabinet. 20 g of pure 7-chloro-1-cyclopropyl-4-oxo-1,4-dihydro-1,6-naphthyridine-3-carboxylic acid of melting point 226° to 227° C. were obtained. (including prevention, relief and cure of) the above-mentioned diseases in warm-blooded animals, which comprises administering to the animals a compound of the invention alone or in admixture with a diluent or in the form of a medicament according to the invention.

The present invention further provides a feed additive comprising an active compound of the present invention in admixture with a feed additive-carrier.

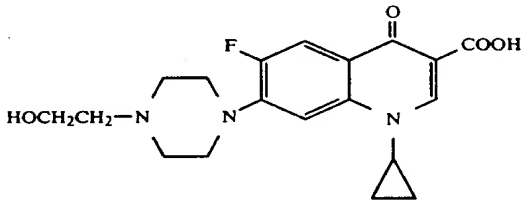
The Examples which follow illustrate the invention further.

EXAMPLE 21



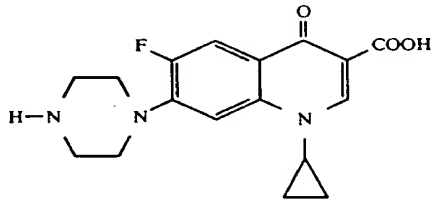
A mixture of 20 g of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, 28.5 g of N-methylpiperazine and 120 ml of anhydrous dimethylsulphoxide was heated at 135° to 140° C. for 1.5 hours. The solvent was distilled off under a fine vacuum, and the residue was suspended in approx. 50 ml of H_2O. The suspension was filtered under suction, and the residue was rinsed with H_2O, dried in a vacuum drying cabinet at 80° C. over $CaCl_2$, and recrystallised from glycol monomethyl ether. 14.5 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-7-(4-methylpiperazino)-4-oxo-quinoline-3-carboxylic acid which decomposes at 248° to 250° C. were obtained.

EXAMPLE 22



A suspension of 2.81 of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and 5.2 g of N-β-hydroxyethylpiperazine in 25 ml of dimethylsulphoxide was heated at 135° to 140° C. for 2 hours. The solvent was distilled off under a fine vacuum, the residue was boiled for a short time with 20 ml of H_2O and left to stand overnight at room temperature, and the precipitate was filtered off under suction, while cooling with ice, and was washed with water and dried in vacuo over $CaCl_2$ at 80° C. 2.1 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-β-hydroxyethyl-piperazino)-quinoline-3-carboxylic acid which decomposed at 237° to 239° C. were obtained.

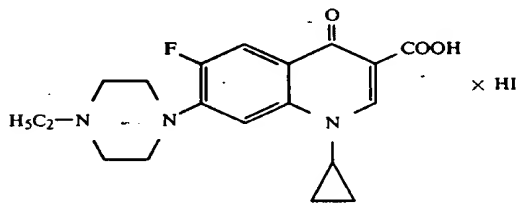
EXAMPLE 23



A mixture of 19.7 g of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, 30.1 g of anhydrous piperazine and 100 ml of dimethylsulphoxide was heated at 135° to 140° C. for 2 hours. The solvent was distilled off under a fine vacuum, and the residue was suspended in H_2O, filtered off under suction and washed with water. For further purification, the moist crude product was boiled with 100 ml of water, filtered off under suction at room temperature, washed with H_2O and dried over $CaCl_2$ in a vacuum drying cabinet at 100° C. until its weight remained constant. 19.6 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid which decomposed at 255° to 257° C. were obtained.

The compound prepared according to Example 3 was dissolved in 50 of hot 10 percent hydrochloric acid. 150 ml of ethanol were added to the filtered solution, the mixture was cooled with ice, and the product was filtered off under suction, washed with alcohol, and dried in vacuo at 100° C. 18.5 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid hydrochloric were obtained as colourless crystals which decomposed at 326°–328° C. The monohydrate of this hydrochloride has a m.p. 318°–320° C.

EXAMPLE 24



(a) A mixture of 1.2 g of 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid, 1.13 g of ethyl iodide, 0.73 g of triethylamine and 20 ml of N,N-dimethylformamide was heated at 70° to 80° C. for 2.5 hours. The solvent was distilled off in vacuo, and the residue was suspended in water. The product was filtered off under suction, rinsed with H_2O and pressed on clay. 1.15 g of 1-cyclopropyl-6-fluoro-7-(ethylpiperazino)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydroiodide which decomposes at 306° C. were obtained.

(b) The 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid used as the starting material was prepared as follows:

24.3 g of magnesium turnings were suspended in 50 ml of anhydrous ethanol. 5 ml of carbon tetrachloride were added and, when the reaction had started, a mixture of 160 g of diethyl malonate, 100 ml of absolute ethanol and 400 ml of anhydrous ether was added dropwise, a vigorous reflux being observed. After the reaction had ceased, the mixture was heated at the boil for a further 2 hours and was cooled with dry ice/acetone at −5° C. to −10° C. and a solution of 227.5 g of 2,4-dichloro-5-fluoro-benzoyl chloride in 100 ml of absolute ether was slowly added dropwise at this temperature. The mixture was stirred for 1 hour at 0° C. to −5° C. and was allowed to reach room temperature overnight, and a mixture of 400 ml of ice-water and 25 ml of concentrated sulphuric acid was allowed to run in while cooling with ice. The phases were separated and were extracted twice with ether. The combined ether solutions were washed with saturated NaCl solution and dried with Na_2SO_4, and the solvent was stripped off in vacuo. 349.5 g of diethyl 2,4-dichloro-5-fluoro-benzoyl-malonate were obtained as the crude product.

0.15 g of p-toluenesulphonic acid was added to an emulsion of 34.9 g of crude diethyl 2,4-dichloro-5-

fluoro-benzoyl-malonate in 50 ml of water. The emulsion was heated at the boil for 3 hours while stirring thoroughly, and, when cold, was extracted several times with methylene chloride, the combined CH_2Cl_2 solutions were washed once with saturated NaCl solution and dried with Na_2SO_4, and the solvent was distilled off in vacuo. Fractionation of the residue under a fine vacuum gave 21.8 g of ethyl 2,4-dichloro-5-fluoro-benzoyl acetate IX of boiling point 127° to 142° C./0.09 mbar.

A mixture of 21.1 g of ethyl 2,4-dichloro-5-fluoro-benzoyl-acetate, 16.65 g of ethyl o-formate and 18.55 g of acetic anhydride was heated at 150° C. for 2 hours. The volatile constituents were then distilled off under a waterjet vacuum and finally under a fine vacuum, at a bath temperature of 120° C. 25.2 g of crude ethyl 2-(2,4-dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylate remained. It was sufficiently pure for the further reactions.

4.3 g of cyclopropylamine were added dropwise to a solution of 24.9 g of ethyl 2-(2,4-dichloro-5-fluoro-benzoyl)-3-ethoxy-acrylate in 80 ml of ethanol while cooling with ice and stirring. When the exothermic reaction had ceased, the mixture was stirred for another hour at room temperature, the solvent was stripped off in vacuo, and the residue was recrystallised from cyclohexane/petroleum ether. 22.9 g of ethyl 2-(2,4-dichloro-5-fluoro-benzoyl)-3-cyclopropylamino-acrylate ($R^1=C_2H_5$) of melting point 89° to 90° C. were obtained.

3.44 g of 80 percent sodium hydride were added in portions to a solution of 31.9 g of ethyl 2-(2,4-dichloro-5-fluoro-benzoyl)-3-cyclopropylamino-acrylate ($R^1=C_2H_5$) in 100 ml of anhydrous dioxane while cooling with ice and stirring. The mixture was then stirred at room temperature for 30 minutes and under reflux for 2 hours, and the dioxane was stripped off in vacuo. The residue (40.3 g) was suspended in 150 ml of water, 6.65 g of caustic potash were added, and the mixture was refluxed for 1.5 hours. The warm solution was filtered and the residue was rinsed with H_2O. The filtrate was then acidified to pH=1 to 2 with semiconcentrated hydrochloric acid, while cooling with ice, and the precipitate was filtered off under suction, washed with water and dried in vacuo at 100° C. 27.7 g of 7-chloro-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid ($R^1=H$) of melting point 234° to 237° C. were obtained in this manner.

The present invention also comprises pharmaceutically acceptable bioprecursors of the active compounds of the present invention.

The following example shows the recipe of a tablet according to the invention:

1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-3-carboxylic acid HCl	277.5 mg	(corresponding to 250.0 mg Butain)
Avicel	49.0 mg	
Moist corn starch	14.0 mg	
Pregelatiniged starch	6.0 mg	
Magnesium stearate	3.5 mg	
tablet without film coating	350.0 mg	
Film coating		
HPM cellulose 15 cp	3.0 mg	
Polyethylene glycol 4000	1.0 mg	
Titanium dioxide	1.0 mg	
film coated tablet	355.0 mg	

For the purpose of this specification the term "pharmaceutically acceptable bioprecursor" of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to a warm-blooded animal is converted in the patient's body to the active compound.

The improved bacterial action of the compounds of Example 1 according to the present invention is particularly clear in the following biotest Example, in which it was compared with 2-piperazino-8-ethyl-5-oxo-5,8-dihydropyrido 2,3-d pyrimidine-6-carboxylic acid ("pipemidic acid") or the known compound 1-ethyl-7-methyl-1,8-naphthyrid-4-one-3-carboxylic acid ["nalidixic acid"; Ehrhart/Ruschig, Arzneimittel (Medicaments), Volume 2: Chemotherapeutika (Chemotherapeutics), Verlag Chemie 1968, page 1,568]. The compounds of the invention have proved to be far superior in vitro and in vivo on bacteria such as Staphylococci, *Escherichia coli*, Proteus, Klebsiella and Pseudomonas than such known compounds.

EXAMPLE

The agar dilution test was carried out by the Denley multipoint inoculation method and the results were as shown in the following Table.

	Minimum inhibitory concentrations mog/ml in an agar dilution test[x]		
	Compounds from Example 1	Pipemidic acid	Nalidixic acid
Escherichia coli			
T 7	0.25	2	1
455/7	128	128	256
103400	0.25	1	2
Salmonella 683	0.5	2	4
Klebsiella 63	1	2	4
Pseudomonas 7167	8	16	64
Proteus 8228	2	4	8

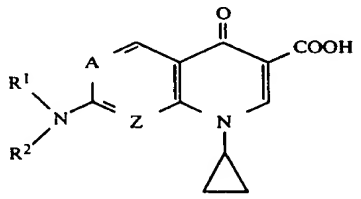
[x]Denley multipoint inoculation method

The present invention also comprises pharmaceutically acceptable bioprecursors of the active compounds of the present invention.

For the purposes of this specification the term 'pharmaceutically acceptable bioprecursor' of an active compound of the invention means a compound having a structural formula different from the active compound but which nonetheless, upon administration to a warm-blooded animal is converted in the patient's body to the active compound.

What is claimed is:

1. A compound which is a 7-amino-1-cyclopropyl-4-oxo-1,4-dihydro-quinoline- and -napthyridine-3-carboxylic acid of the formula



(I)

or a pharmaceutically acceptable acid addition salt or an alkali or alkaline earth metal salt thereof,

in which A represents a nitrogen atom or CR^3,

wherein R^3 denotes a hydrogen, a nitro group or a halogen atom, or a carboxamide or carboxyl group, and

Z represents a nitrogen atom or C—H, and A and Z cannot simultaneously be nitrogen atoms, and R^1

and R^2 are identical or different and represent a hydrogen atom or a straight-chain or branched alkyl, alkenyl or alkinyl radical which has up to 12 carbon atoms and is optionally substituted by radical(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms in each alkyl radical, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bicyclic carbocyclic aryl, or furthermore represents a cycloalkyl radical with 3 to 6 carbon atoms, or, together with the nitrogen atom which they substituted or together with a further hetero-atom selected from the group consisting of N, O and S form a 3-membered to 7-membered ring which can be substituted by radical(s) selected from alkyl or alkenyl with 1 to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carbocyclic aryl.

2. A compound according to claim 1, in which A represent CR^3 and R^3 represents a fluorine or chlorine atom.

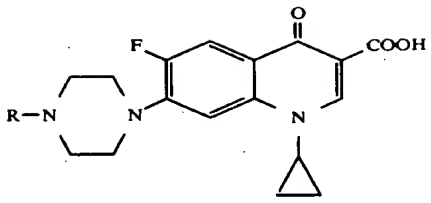
3. A compound according to claim 1 or 2, in which R^1 and R^2 together with the nitrogen atom which they substituted and oxygen, sulphur or R^4-substituted nitrogen as a further hetero-atom form a 3-membered or 7-membered ring which may be substituted by radical(s) selected from alkyl or alkenyl with up to 6 carbon atoms, hydroxyl, alkoxy or alkylmercapto with 1 to 3 carbon atoms, alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, and mono- or bi-cyclic carboxylic aryl,

and in which R^4 represents a hydrogen, or an unsubstituted branched or straight-chain alkyl group which has up to 6 carbon atoms or a branched or straight-chain alkyl which has up to 6 carbon atoms which is substituted by radicals(s) selected from hydroxyl, alkoxy, alkylmercapto or dialkylamino with 1 to 3 carbon atoms per alkyl radical, and alkoxycarbonyl with 1 to 4 carbon atoms in the alcohol part, or represents an phenylalkyl group which has up to 4 carbon atoms in the aliphatic part, or an optionally substituted phenyl or naphthyl group or pyridine, pyrimidine, thiazole or benzothiazole, or

R^4 denotes an alkoxycarbonyl group which is optionally substituted by a mono- or bi-cyclic carbocyclic aryl radical and has 1 to 4 carbon atoms in a alcohol part an alkanoyl radical with 1 to 6 carbon atoms, a benzoyl or naphthoyl radical, an alkyl-, phenyl- or naphthyl-(thio) carbamoyl radical, an alkyl-, phenyl- or naphthyl-sulphonyl radical or an aminosulphonyl radical.

4. A compound according to claim 3, in which R^4 represents a radical of pyridine, pyrimidine, thiazole or benzothiazole.

5. A 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid of the formula



(I)

or salts and/or hydrates thereof,

in which R denotes hydrogen, methyl, ethyl or β-hydroxyethyl.

6. A compound according to claim 1 which is 7-(4-methylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

7. A compound according to claim 1 which is 7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

8. A compound according to claim 1 which is 7-pyrrolidino-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

9. A compound according to claim 1 which is 7-(4-formylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

10. A compound according to claim 1 which is 7-(4-hydroxyethylpiperazino)-1-cyclopropyl-4-oxo-1,4-dihydro-naphthyridine-3-carboxylic acid.

11. A compound according to claim 1 which is 7-piperazino-1-cyclopropyl-4-oxo-1,4-dihydro-6-fluoro-quinoline-3-carboxylic acid.

12. A compound of claim 5 which is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-piperazino-quinoline-3-carboxylic acid.

13. A compound of claim 5 which is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-methylpiperazino)-quinoline-3-carboxylic acid.

14. A compound of claim 5 which is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-ethylpiperazino)-quinoline-3-carboxylic acid.

15. A compound of claim 5 which is 1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(4-β-hydroxyethyl-peperazino)-quinoline-3-carboxylic acid.

16. A pharmaceutical composition containing as an active ingredient an antibacterially effective amount of a compound according to claim 1 in admixture with an inert pharmaceutical carrier.

17. A pharmaceutical composition according to claim 16 in the form of a sterile or physiologically isotonic aqueous solution.

18. A composition according to claim 16 or 17 containing from 0.5 to 95% by weight of the said active ingredient.

19. A medicament in dosage unit form comprising an antibacterially effective amount of a compound according to claim 1 together with an inert pharmaceutical carrier.

20. A medicament of claim 18 in the form of tablets, pills, dragees, capsules, ampoules, or suppositories.

21. A method of combating bacterial illnesses in warm-blood animals which comprises administering to the animals an antibacterially effective amount of an active compound according to claim 1 either alone or in admixture with a diluent or in the form of a medicament.

22. An animal feed, food concentrate or drinking water comprising an active compound according to claim 1.

* * * * *

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Klaus Grohe, et al.
SERIAL NO.	:	614,923
FILED	:	May 29, 1984
TITLE	:	7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS
PATENT No.	:	4,670,444
ISSUED	:	June 02, 1987

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

TERMINAL DISCLAIMER

Bayer Aktiengesellschaft of Leverkusen, Germany, by its undersigned authorized officers represents that it is the assignee (Assignment recorded at Reel 4301, Frame 557) of U.S. Patent No. 4,670,444, filed on May 29, 1984 and issued on June 02, 1987. Bayer Aktiengesellschaft hereby disclaims the terminal part of U.S. Patent No. 4,670,444 which extends beyond October 01, 2002, the earlier of the expiration dates of U.S. Patents Nos. 4,544,658 (issued October 01, 1985) and 4,556,658 (issued December 03, 1985), and hereby agrees that U.S. Patent No. 4,670,444 shall be enforceable only for and during such period that legal title to U.S. Patent No. 4,670,444 shall be the same as legal title to U.S. Patent Nos. 4,544,658 and 4,556,658, this agreement to run with U.S. Patent No. 4,670,444 and to be binding upon the grantee, its successors or assigns.

Dated: February 18, 1992

Respectfully submitted

BAYER AKTIENGESELLSCHAFT
Leverkusen, Germany

(ppa Dänner)
Secretary

(ppa Schauerte)
Secretary

ATTACHMENT "B"

ATTACHMENT "C"

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS	:	Klaus Grohe, et al.
SERIAL NO.	:	614,923
FILED	:	May 29, 1984
TITLE	:	7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE-AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS
PATENT NO.	:	4,670,444
ISSUED	:	June 2, 1987

The Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

AMENDED TERMINAL DISCLAIMER

Sir:

Petitioner, Bayer Aktiengesellschaft of Leverkusen, Germany, by its undersigned authorized officers represents that it is the assignee (assignment recorded at Reel 4301, Frame 557) of U.S. Patent No. 4,670,444, filed on May 29, 1984 and issued on June 2, 1987.

Petitioner hereby disclaims the terminal part of the full statutory term as defined in 35 U.S.C. §§ 154 - 156 and 173 of U.S. Patent No. 4,670,444 which would extend beyond the earlier of the expiration dates of the full statutory term as defined in 35 U.S.C. §§ 154 - 156 and 173 of U.S. Patent Nos. 4,544,658 (filed December 9, 1983 and issued October 1, 1985) and 4,556,658 (filed April 24, 1984 and issued December 3, 1985), as presently shortened by any terminal disclaimer. Petitioner hereby agrees that U.S. Patent No. 4,670,444 shall be enforceable

only for and during such period that legal title to U.S. Patent No. 4,670,444 shall be the same as legal title to U.S. Patent Nos. 4,544,658 and 4,556,658. This agreement runs with U.S. Patent No. 4,670,444 and is binding upon the grantee, its successors or assigns.

In making the above disclaimer, Petitioner does not disclaim the terminal part of U.S. Patent No. 4,670,444 that would extend to the earlier expiration date of the full statutory terms as defined in 35 U.S.C. §§ 154 to 156 and 173 of U.S. Patent Nos. 4,544,658 and 4,556,658, as presently shortened by any terminal disclaimer, in the event that they later: expire for failure to pay a maintenance fee, are held unenforceable, are found invalid by a court of competent jurisdiction, are statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. 1.321, have all claims canceled by a reexamination certificate, are reissued, or are in any manner terminated prior to the expiration of their full statutory terms.

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of U.S. Patent No. 4,670,444.

Respectfully submitted,

BAYER AKTIENGESELLSCHAFT

Leverkusen, Germany

Date: June 30, 1995

By: _____

Title: Director

By: _____

Title: Secretary

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,670,444

DATED : June 2, 1987

INVENTOR(S) : Klaus Grohe, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 2, line 7	After "preferably 1" insert --or--
Col. 2, line 15	Delete "aryl" and substitute --aroyl--
Col. 2, lines 34-35	Correct spelling of --monosubstituted--
Col. 4, line 34	Delete "(IV)" and substitute --(VI)--
Col. 8, line 67	Delete "5-dichloro-"
Col. 9, line 8	Delete "(XIII)" and substitute --(XII)--
Col. 10, line 28	After "methyl" delete ":" and substitute -- - --
Col. 13, line 34	Correct spelling of --sorbitol--
Col. 15, Table 1 con't, last column heading	Delete "(°C)" and substitute --(°C)-- 306
Col. 15, Table 1 con't Ex. No. 7, last column	Insert --306-- above "(hydrochloride)"
Col. 15, Table 1 con't	Delete Example Nos. "1 to 9" and substitute --11 to 19--
Col. 18, line 10	After "50" insert --ml--
Col. 18, line 17	Delete "hydrochloric" and substitute --hydrochloride--
Col. 20, line 1	Delete "purpose" and substitute --purposes--

ATTACHMENT "D"

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 4,670,444

DATED : June 2, 1987

INVENTOR(S) : Klaus Grohe, et al.

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Col. 21, line 36	Delete "carboxylic" and substitute --carbocyclic--
Col. 21, line 56	Before "alcohol" delete "a" and substitute --the--

Signed and Sealed this

Fifteenth Day of March, 1988

Attest:

Attesting Officer

DONALD J. QUIGG

Commissioner of Patents and Trademarks

ATTACHMENT G

Table of Contents

Chronology of Labeling Development

8/26/86 - Draft labeling was included with the submission of the Original New Animal Drug Application (NADA 140-828) with the indications for use in turkey drinking water for the control of fowl cholera in growing turkeys - susceptibility and pharmacokinetic data were included in the submission

5/29/87 - Letter from CVM stating that there were no adverse comments regarding the labeling - suggestion to revise the net contents statement

11/30/89 - In an amendment to the NADA to provide data to support use of the product in chicken drinking water for the control of colibacillosis in chickens, revised draft labeling was submitted with the indications for use in chicken and turkey drinking water

9/1/92 - Draft labeling was submitted to CVM with the revision to include the restriction against using the product in chickens or turkeys intended for breeding or laying purposes

3/11/93 - CVM responded that the label may need further revisions to reflect the Target Animal Safety data and pending human food safety studies

10/19/94 - Revised labeling was included with the Baytril 3.23% Concentrate Solution Phased Chemistry submission - revisions included changes to a prescription drug format; change in the indications to add a claim for colibacillosis in turkeys; change to a range in dosage and treatment duration (25-50 ppm for 3-7 days) - no label changes resulted from the chemistry review

10/28/94 - Draft labeling was also included in the Phased Efficacy submission to the chicken INAD - 4586

11/11/94 - Draft labeling was included in the Phased Efficacy submission to the turkey INAD - 4368

6/14/95 - Letter from CVM (PEF 4586 A-0000) with comments resulting from the review of the chicken water phased efficacy submission - comments included minor text changes as well revisions to the WARNING section to include specifics of user safety and the addition of a telephone number for additional information or Material Safety Data Sheet

8/8/95 - Letter from CVM (PEF 4368 A-0000) with comments resulting from the review of the turkey phased efficacy submission - comments were similar to those in the 6/14/95 review letter

12/14/95 - Revised draft labeling was submitted to CVM including changes resulting from the phased efficacy review letters - also, removed the contraindication against use of the product in chickens or turkeys intended for breeding or laying purposes as a result of the reproductive safety study submitted to CVM on 10/13/95 - added a statement against use in laying hens producing eggs for human consumption and a one day withdrawal statement

2/6/96 - Submission to INAD's 4368 and 4586 of enrofloxacin *in vitro* susceptibility data for poultry to provide baseline susceptibility data on poultry pathogens

4/22/96 - Submission to both poultry INAD's of data from pharmacokinetic studies in growing chickens and growing turkeys in order to support proposed label statements

4/24/96 - Letter from CVM (INAD 4586 H-0058) containing comments concerning the reproductive safety study in chickens stated that no restrictive label statement cautioning against use of the product in chickens intended for breeding purposes would be required, however, the indications for chickens would be limited to use in growing broilers and growing broiler breeder replacements and a restrictive statement would still be necessary concerning the use of the product in turkeys intended for breeding purposes unless a similar reproductive study was submitted and accepted for turkeys

5/30/96 - Additional susceptibility data was submitted to CVM under both INAD's

5/7/96 - Bayer representatives met with CVM personnel to discuss the label

6/27/96 - Bayer submitted justification for the proposed indications for use of the product in chicken and turkey drinking water and facsimile labeling with these indications

7/22/96 - Letter from CVM (INAD 4368 H-0061, G-0065, H-0070 & INAD 4586 H-0069, H-0073, H-0078), which referred to our submissions of *in vitro* susceptibility data, stated that we had submitted an adequate number of isolates for labeling purposes and the data were appropriate for inclusion in the labeling

8/7/96 - Letter from CVM (INAD 4368 Y-0075 & INAD 4586 Y-0083) stated that the proposed indications were acceptable as they appeared in the facsimile

labeling provided a statement against use of the product in laying hens producing eggs for human consumption was added to the front panels of the unit labels and package insert

8/16/96 - Facsimile labeling was submitted which contained the additional warning as specified in the 8/7/96 letter from CVM as well as a revised Pharmacokinetics section and additional statements in the Dosage and Administration section using text supplied by CVM in a fax dated 8/7/96

9/5/96 - Facsimile labeling was submitted to CVM containing revisions requested by the reviewer in a telephone conversation on September 4, 1996

9/10/96 - Letter from CVM (INAD 4368 G-0083 & INAD 4586 G-0093) stated that the revised draft facsimile labeling was acceptable

Manufacturing Methods, Facilities and Controls

Chronology

8/26/86 - A complete Chemistry, Manufacturing and Controls technical section was submitted in the original New Animal Drug Application (NADA 140-828) for use of Baytril 3.23% Concentrate Solution in turkey drinking water - including all documentation required in the components and composition section - all information included in the original NADA supported the 25 ppm dosage rate

11/30/89 - Amendment submitted to NADA 140-828 to provide data to support claims for use of the product in chicken drinking water - submission included an update of the manufacturing and controls section

5/13/94 - Bayer representatives met with CVM personnel to discuss requirements needed to complete the phased chemistry component of the NADA for a proposed dosage range of 25 - 50 ppm for a duration of 3 to 7 days - Bayer presented a brief review of previously submitted components, and discussion of components to be submitted for the phased chemistry review, including new methods and validation data, studies to support the proposed dosage range, and bridging studies to compare pilot and production batches and to compare the new analytical methods with the previous ones

8/2/94 - Submission of VMF-5513 containing information describing the current manufacturing and control procedures used in the production of enrofloxacin drug substance

10/19/94 - Phased Manufacturing Chemistry technical section was submitted to the INAD's for turkey and chicken water (4368 and 4586), which included the following:

a. additional documentation to support the proposed dosage range
b. update previously submitted documentation, including a reference to the enrofloxacin drug master file (VMF-5513)
c. studies bridging the previously submitted data with new data
d. a response to the CVM comment pertaining to the finished product release specifications
e. copies of the previously submitted documents from sections 4 and 5 of the NADA to aid the reviewer

1/23/95 - CVM responded with comments to the enrofloxacin drug master file which was submitted to support the phased chemistry component

3/27/95 - CVM responded to the phased chemistry submission with an incomplete letter with comments on several analytical methods and stability information

5/12/95 - Submission from Bayer with responses to CVM's 3/27/95 letter

5/23/95 - Bayer provided a submission responding to CVM's 1/23/95 letter regarding the drug master file

7/20/95 - A letter from CVM stated that the information submitted to VMF-5513 was acceptable

11/9/95 - A letter from CVM stated that the Chemistry, Manufacturing and Controls phased technical section was complete

Analytical Methods for Residues

Chronology

8/20/86 - Residue chemistry master file (VMF-5111) established to reference as support for several INAD's and NADA's pertaining to the use of enrofloxacin in poultry

8/26/86 - Original New Animal Drug Application submitted for Baytril 3.23% Concentrate Solution for turkeys (NADA 140-828) - all data and reports referenced were contained in VMF-5111

11/30/89 - Amendment submitted to NADA 140-828 to include data to support use of the product in chickens - additional data was submitted to VMF-5111 on turkeys as well as residue and metabolism data pertaining to chickens

6/10/94 - Letter submitted to CVM stating that new residue studies would be performed to: treat birds more in-line with the age and size treated in the field; to use better methodology available; and to generate additional tissues to use in the new determinative method - the information in VMF-5111 would be referenced as corroborative data only

12/12/94 - Letter from CVM stated that it would be easier administratively to submit new studies directly to the pertinent INAD's

3/23/95 - Phased Marker Residue Methodology packages were submitted to both INAD 4368 and 4586, including the determinative method, confirmatory method and method validation studies

7/25/95 - Letter from CVM (I-004368-P-0044 and I-004586-P-0042) providing comments from their review of the proposed determinative and confirmatory methods submitted 3/23/95

9/18/95 - In letters to each INAD, Bayer notified CVM of their intention to follow the sponsor-managed validation process and provided a draft protocol for the validation of the determinative method

10/6/95 - CVM responded with comments to the draft protocol submissions for the sponsor-managed method trial

1/31/96 - Bayer provided responses to CVM's 7/25/95 letter reviewing the residue chemistry methods

3/4/96 - Bayer provided submissions to the chicken and turkey INAD's with draft protocols for the sponsor-managed method trial revised to address comments in CVM's 10/6/95 letter

3/27/96 - CVM responded to the 3/4/96 draft protocols and provided additional comments

4/2/96 - CVM provided comments to the revised determinative and confirmatory procedures submitted 1/31/96

5/22/96 - Bayer provided updated determinative and confirmatory methods as well as responses to CVM's 4/2/96 letter

5/23/96 - Bayer provided responses to CVM's comments in their 3/27/96 letter on the protocol for the sponsor-managed method validation, including a revised draft protocol for review

6/28/96 - Letter from CVM (I-004368-H-0068 and I-004586-H-0076) stated that the analytical method for the determination and confirmation of enrofloxacin in poultry muscle was adequate to schedule the method demonstration

7/1/96 - Letter from CVM (I-004368-E-0069 and I-004586-E-0077) stated that the revised draft protocol for the sponsor-managed method trial was adequate to schedule the method demonstration because the determinative method was considered adequate and the tentative tolerance had been set

8/2/96 - Bayer submitted copies of the final signed protocol for the sponsor-managed method validation which included changes agreed upon during the method demonstration

9/13/96 - Bayer submitted copies of three reports documenting the successful validation of the analytical residue method following the sponsor-managed validation process

Target Animal Safety

Chronology

8/26/86 - A complete Target Animal Safety section was included in the submission of NADA 140-828

5/29/87 - In a response letter, CVM stated that the safety for treating turkeys at a dose of 25 ppm for 5 to 7 days was adequate

11/30/89 - In an amendment to NADA 140-828, target animal safety data was submitted to support use of the product in growing chickens

10/2/91 - In CVM letter 140-828 E004, it was stated that existing target animal safety studies for enrofloxacin were acceptable only for nonbreeding broilers and growing turkeys

11/2/94 - Published literature relevant to enrofloxacin use in chickens was submitted to the Agency to both chicken and turkey water INAD's

11/15/94 - Submissions to INAD 4368 and 4586 were made of all foreign/related safety reports

6/14/95 - In a response letter to INAD 4586 (PEF 4586 A-0000), CVM stated that requirements for target animal safety were complete for the product in chickens over a proposed dosage range of 25 to 50 ppm for 3 to 7 days

8/8/95 - In a separate letter to INAD 4368 (PEF 4368 A-0000), CVM again stated that they considered the requirements for target animal safety to be complete for doses up to 50 ppm administered to turkeys for a duration up to 7 days

10/13/95 - Bayer submitted a reproductive safety evaluation for Baytril 3.23% in broiler breeders - the study concluded that the treatment of male and female broiler chickens with the product at a rate of 150 ppm for 7 consecutive days at up to 5 intervals during the growth and reproductive stages had no adverse effects upon reproductive parameters

4/24/96 - In a letter to INAD 4586 (INAD 4586 H-0058), CVM stated that the reproductive study supported the safety of Baytril 3.23% Concentrate Solution when used in broiler breeder chickens of both sexes for the proposed label dose of 25 to 50 ppm for a maximum of 7 days - also, a

restrictive label statement will be necessary concerning use of the product in turkeys intended for breeding purposes unless a similar study is conducted and accepted for turkeys

Target Animal Effectiveness

Chronology

11/20/84 - Established an INAD (4368) for investigation of the use of enrofloxacin in turkeys

9/30/85 - Established an INAD (4586) for investigation of the use of enrofloxacin in chickens

8/26/86 - New Animal Drug Application (NADA 140-828) was submitted to CVM which included efficacy data from a dose sighting study, dose titration and dose confirmation studies - also included susceptibility and pharmacokinetic data

5/29/87 - Letter from CVM stated that it had been adequately demonstrated that the drug is effective in controlling fowl cholera in growing turkeys at the recommended level of 25 ppm continuously in the drinking water for 5 to 7 days

11/30/89 - Amendment submitted to NADA 140-828 to include data to support use of the product in chickens

5/9/90 - In a response letter to the NADA, CVM stated that the submitted efficacy studies were considered satisfactory - this statement was repeated in letters dated 10/2/91 and 3/11/93

5/18/93 - Bayer representatives met with CVM personnel to establish the requirements needed to expand the proposed label for both chickens and turkeys by establishing a dosage range of 25 to 50 ppm and expanding the treatment duration to 3 to 7 days, to add a claim against *E. coli* in turkeys, and to remove the restriction against use in breeding and laying birds

10/28/94 - Phased efficacy submission was made to INAD 4586 providing data to support the effectiveness of the product in controlling *E. coli* infections in broiler chickens at a rate of 25 ppm for 3 days - also included a volume of non-pivotal foreign reports

11/2/94 - Submission to INAD 4586 of published literature pertaining to the use of enrofloxacin in chickens

11/11/94 - Submission to INAD 4368 of published literature pertaining to the use of enrofloxacin in turkeys

11/11/94 - Phased efficacy submission was made to INAD 4368 providing data to support the effectiveness of the product in controlling fowl cholera in turkeys at a rate of 25 ppm for 3 days and to establish the effectiveness of the product for control of colibacillosis in turkeys - also included non-pivotal foreign reports

6/14/95 - Letter from CVM with comments on the Phased Efficacy submission to INAD 4586 stating that the information from the clinical field trials completed the efficacy component expanding the dose range to 25 to 50 ppm for 3 to 7 days - also contained comments on the efficacy section of the FOI and label

8/8/95 - Letter from CVM with comments on the Phased Efficacy submission to INAD 4368 stating that the efficacy component for a dose range of 25 to 50 ppm administered for 3 to 7 days was complete - also contained comments on the statistical analyses, FOI and label

2/6/96 - Submission to INAD 4368 and INAD 4586 containing enrofloxacin *in-vitro* susceptibility data for poultry to provide baseline susceptibility data on poultry pathogens

4/22/96 - Submission to both poultry INAD's of data from pharmacokinetic studies in growing chickens and growing turkeys in order to support proposed label statements

5/30/96 - Additional susceptibility data was submitted to CVM under both INAD's

6/21/96 - Separate submissions to each INAD of updated published literature pertaining to the use of enrofloxacin in poultry

7/12/96 - Separate submissions to each INAD of updated non-pivotal foreign reports pertaining to the use of enrofloxacin in poultry

Chronology of Toxicology

9/30/85 - Established a basic toxicology master file, VMF-5057, to support several INAD's and NADA's pertaining to enrofloxacin - master file was updated periodically as additional data was obtained

8/26/86 - Original New Animal Drug Application submitted for Baytril 3.23% Concentrate Solution for turkeys (NADA 140-828) - VMF-5057 was referenced for basic toxicology data

11/30/89 - Amendment submitted to NADA 140-828 to include data to support use of the product in chickens - reference to VMF-5057 for additional data submitted to the master file

2/8/94 - Phased data submission made to VMF-5057 along with a request for Agency concurrence that a no-observable effect of at least 100 ppm was achieved for both male and female rats in the chronic toxicity studies and a concurrence that all basic toxicology requirements for NADA purposes were fulfilled

7/22/94 - Letter from CVM stated that the submitted data established a NOEL for both male and female rats as 100 ppm relative to the lesion of bile duct hyperplasia

10/11/94 - Letter from CVM to VMF-5057 stated that the human food safety toxicology package for enrofloxacin for use in beef cattle is complete - this package was also referenced for the poultry claims of enrofloxacin - the 13-week oral toxicity study in dogs was the most appropriate study submitted to base the safe concentration of the total residues of enrofloxacin in food animal tissues and products - the NOEL was set at 100 ppm; the ADI was set at 0.003 mg/kg of body wt./day; and the safe concentration was calculated as 0.60 ppm for muscle

9/27/95 - Letter to CVM referencing both poultry INAD's provided summary reports constituting the basic toxicology of enrofloxacin to support user safety - also included a Material Safety Data Sheet for the drug substance and a proposed label statement regarding user safety

12/19/95 - CVM responded to the user safety submission with a revised proposed label statement - labeling was revised at that point to include the CVM proposed label statements

Chronology of Residue Chemistry Technical Section

8/20/86 - Residue chemistry master file (VMF-5111) established to reference as support for several INAD's and NADA's pertaining to the use of enrofloxacin in poultry

8/26/86 - Original New Animal Drug Application submitted for Baytril 3.23% Concentrate Antimicrobial Solution for turkeys (NADA 140-828) - all data and reports referenced were contained in VMF-5111

11/30/89 - Submitted an amendment to NADA 140-828 to include data to support use of the product in chickens - additional data was submitted to VMF-5111 on turkeys as well as residue and metabolism data pertaining to chickens

6/10/94 - Letter submitted to CVM stating that new residue studies would be performed to: treat birds more in-line with the age and size treated in the field; to use better methodology available; and to generate additional tissues to use in the new determinative method - the information in VMF-5111 would be referenced as corroborative data only

12/12/94 - Letter from CVM stated that it would be easier to submit the new studies directly to the pertinent INAD

4/19/95 - Separate Phased Metabolism/Residue Depletion submissions made to INAD 4368 and INAD 4586 - the studies determined that the target tissue is muscle and the marker residue is enrofloxacin

5/3/96 - Responses received from CVM (INAD 4368 P0046 and INAD 4586 P 0044) on the turkey and chicken phased residue and metabolism submissions containing specific questions concerning several studies in the submissions

6/6/96 - Submission to INAD 4368 with responses to CVM's questions on the phased residue chemistry submission

6/19/96 - Submission to INAD 4586 with responses to CVM's questions concerning the phased residue chemistry submission

7/18/96 - Letters from CVM to both the chicken and turkey INAD's (INAD 4586 P0081 and INAD 4368 H0073) stating that Bayer had completed the

residue chemistry study requirements for the human food safety portion of the NADA. CVM made the following assignments: muscle is the target tissue and enrofloxacin is the marker residue; 0.3 ppm is the tolerance for residues in chicken and turkey muscle; and the withdrawal time is two days. The tolerance and withdrawal time are contingent upon their acceptance of the determinative assay.

Environmental Assessment

Chronology

8/22/86 - Established an environmental chemistry master file (VMF-5112) to be referenced in support of enrofloxacin NADA's

8/26/86 - Original New Animal Drug Application submitted for Baytril 3.23% Concentrate Solution for use in Turkey drinking water (NADA 140-828) - included an environmental assessment with a reference to reports in VMF-5112

5/29/87 - CVM provided comments to their review of the NADA submission - including comments to the environmental assessment - in later discussions with CVM, Bayer was advised to submit revisions to the INAD's

11/16/89 - Submissions were made to INAD's 4368 and 4586 of a revised EA which addressed comments in CVM's 5/29/87 letter and to include information for use in chicken drinking water

4/1/91 - Letter from CVM containing comments on the EA submitted 11/16/89

8/6/93 - Bayer representatives met with CVM personnel to discuss environmental assessments - decision was made that any additional studies would be submitted to the INAD's - additional studies were submitted over a two year period for review by CVM

3/7/96 - Environmental assessment submitted to CVM for review and was based on numerous toxicology, metabolism, residue, environmental fate and environmental effects studies reviewed and accepted by CVM

6/18/96 - 6/19/96 Letters from CVM to INAD's 4586 and 4368 provided a review of the EA submitted 3/7/96 and stated that the environmental safety technical section was complete with a request that a final paper copy and electronic copy of the EA be submitted along with a statement that the EA is equivalent to the version previously reviewed

8/2/96 - Submission to CVM of the final version of the enrofloxacin environmental assessment for poultry with a description of the minor change made to one page of the EA

9/6/96 - Letter from CVM acknowledging the receipt of the final version of the EA, noting the one minor change from the previously reviewed version. The letter stated that the environmental safety technical section of the application is complete. A copy of the Finding of No Significant Impact statement (FONSI) was attached

9/12/96 - An electronic copy of the final version of the EA was submitted to CVM

Enrofloxacin Environmental Studies

Environmental Fate Studies

Report Title	Report No.	CVM Response	
"Hydrolysis of ^{14}C-Enrofloxacin in Buffered Aqueous Solutions"	106423	VMF 5112 C-0008	2/28/95
"Hydrolysis of ^{14}C-Ciprofloxacin in Buffered Aqueous Solutions"	106430	VMF 5112 C-0008	2/28/95
"Physical Chemical Properties of Ciprofloxacin"	106436	INAD 4586 P-0040	11/2/95
"Sorption/Desorption of ^{14}C-Enrofloxacin on Soils by the Batch Equilibrium Method"	106555	INAD 4586 P-0040	11/2/95
"Sorption/Desorption of ^{14}C-Ciprofloxacin on Soils by the Batch Equilibrium Method"	106556	INAD 4586 P-0040	11/2/95
"Sorption/Desorption of ^{14}C-Enrofloxacin in Cattle Manure and Poultry Excreta and ^{14}C-Ciprofloxacin in Cattle Manure"	106557	INAD 4586 P-0040	11/2/95
"Aerobic Biodegradation of [4-^{14}C] Enrofloxacin in Soil and Feces"	106560	INAD 4586 P-0040	11/2/95
"Aerobic Biodegradation of [4-^{14}C] Ciprofloxacin in Soil"	106561	INAD 4586 P-0040	11/2/95
"Biodegradation of ^{14}C-Enrofloxacin and ^{14}C-Ciprofloxacin by *Aspergillus clavatus, Cunninghamella elegans, Trichoderma hamatum, and Phanerochaete chrysosporium*"	106772	INAD 4586 P-0040	11/2/95
"Analysis of [2,3-Piperazinyl $^{13}C_2$]/[4-^{14}C] Enrofloxacin Residues in Chicken Excreta"	106937	INAD 4586 P-0054	1/11/96
"Photodegradation of [4-^{14}C] Enrofloxacin in Sterile Buffer"	106562	INAD 4586 P-0054	1/11/96
"Photodegradation of [4-^{14}C] Ciprofloxacin in Sterile Buffer"	106563	INAD 4586 P-0054	1/11/96
"Analysis of [2,3-Piperazinyl $^{13}C_2$]/[4-^{14}C] Enrofloxacin Residues in Turkey Excreta"	106632	INAD 4586 H-0053	11/2/95
"Water Solubility of BAY Vp 2674"	73353	VMF-5112	1/16/87
"Vapor Pressure of BAY Vp 2674"	73409	VMF-5112	1/16/87
"n-Octonal/water partition coefficient for BAY Vp2674"	73390	VMF-5112	1/16/87
"Dissociation Constant for Enrofloxacin (Bay Vp 2674)"	73955	VMF-5112	4/1/91

"Absorption Spectra for Enrofloxacin (Bay Vp 2674)"	73954	VMF-5112	4/1/91
"Soil Adsorption Constant for Enrofloxacin, BAY Vp 2674"	73742	VMF-5112	4/1/91

Ecological Effects

Report Title	Report No.	CVM Response	
"Acute Toxicity of Enrofloxacin to the Rainbow Trout(*Oncorhynchus mykiss*) Under Static Renewal Conditions"	74501	VMF 5112 C-0009 VMF 5112 C-0011	4/19/95 2/14/96
"Acute Toxicity of Enrofloxacin to the Bluegill *(Lepomis macrochirus)* Under Static Renewal Conditions"	74507	VMF 5112 C-0009 VMF 5112 C-0011	4/19/95 2/14/96
"Acute Toxicity of Ciprofloxacin to the Rainbow Trout (*Oncorhynchus mykiss*) Under Static Renewal Conditions"	106775	VMF 5112 C-0009 VMF 5112 C-0011	4/19/95 2/14/96
"Acute Toxicity of Ciprofloxacin to the Bluegill *(Lepomis macrochirus)* Under Static Renewal Conditions"	106791	VMF 5112 C-0009 VMF 5112 C-0011	4/19/95 2/14/96
"Biological Effects of enrofloxacin on rainbow trout, bluegill sunfish and daphnia"	73694	VMF-5112	4/1/91
"Acute Toxicity of Enrofloxacin to *Daphnia magna*"	106595	INAD 4586 H-0037	7/31/95
"Chronic Toxicity of Enrofloxacin to *Daphnia magna*"	106790	INAD 4586 H-0037	7/31/95
"Acute Toxicity of Ciprofloxacin to *Daphnia magna*"	106596	INAD 4586 H-0037 INAD 4586 G-0053	7/31/95 12/20/95
"Acute Toxicity of Enrofloxacin to *Hyalella azteca*"	106788	INAD 4586 H-0037	7/31/95
"Acute Toxicity of Ciprofloxacin to *Hyalella azteca*"	106783	INAD 4586 H-0037	7/31/95
"Effect of Ciprofloxacin Technical on Growth of the Green Alga (*Selanastrum capricornutum*)"	106633	INAD 4586 P-0041 INAD 4586 G-0065	9/6/95 2/9/96
"Effect of Enrofloxacin Technical on Growth of the Green Alga (*Selanastrum capricornutum*)"	106657	INAD 4586 P-0041 INAD 4586 G-0065	9/6/95 2/9/96
"Subacute Toxicity of Ciprofloxacin to the Earthworm *Lumbricus terrestris*"	106793	INAD 4586 P-0041	9/6/95
"Toxicity of Enrofloxacin (Bay Vp 2674) to Earthworms (*Lumbricus terrestris*)	74123	INAD 4586 P-0041 INAD 4586 G-0065	9/6/95 2/9/96
Subacute Toxicity of Enrofloxacin (Bay Vp 2674) to Earthworms (*Lumbricus terrestris*)	73584	INAD 4586 P-0041	9/6/95

"FDA Seedling Growth Phytotoxicity Test with Enrofloxacin"	74583	INAD 4586 P-0052	1/25/96
"Growth Rate Effect of ^{14}C-Enrofloxacin to *Microcystis aeruginosa*"	106940	INAD 4586 P-0052	1/25/96
"Growth Rate Effect of ^{14}C-Ciprofloxacin to *Microcystis aeruginosa*"	106627	INAD 4586 P-0052	1/25/96
"Seed Germination and Root Elongation Study Using Enrofloxacin"	106661	INAD 4586 P-0046	12/21/95
"Seed Germination and Root Elongation Study Using Ciprofloxacin"	106911	INAD 4586 P-0046	12/21/95
"Soil Seed Germination and Root Elongation Study Using Enrofloxacin"	74576	INAD 4586 P-0046	12/21/95
"Microbial Growth Inhibition with Enrofloxacin"	106599	INAD 4586 P-0040	11/2/95
"Microbial Growth Inhibition with Ciprofloxacin"	106750	INAD 4586 P-0040	11/2/95
"FDA Seedling Growth Phytotoxicity Test with Enrofloxacin and Ciprofloxacin"	74511	INAD 4586 H-0062	2/9/96
"Bioavailability of Enrofloxacin in Soil and Manure and its Effect on Microbial Growth Inhibition"	107124	INAD 4586 H-0062	2/9/96

Freedom of Information Summary

Chronology

8/26/86 - Submission of New Animal Drug Application (NADA 140-828) for the use on enrofloxacin in turkey drinking water - included a draft FOI

5/29/87 - Letter from CVM containing a review of the NADA - included several comments regarding the FOI

11/30/89 - Amendment to NADA 140-828 to provide data to support use of the product in chicken drinking water - also provided a revised FOI summary to address the additional claims and revisions per comments in CVM's 5/29/87 letter

11/9/93 - Letters from CVM to both chicken and turkey INAD's providing comments regarding the Target Animal Safety section of the FOI's

10/28/94 - Phased efficacy submission to the chicken drinking water INAD (4586) including a draft FOI of general information and efficacy information

11/11/94 - Phased efficacy submission to the turkey drinking water INAD (4368) including a draft FOI of general information and efficacy information

6/14/95 - Letter from CVM to INAD 4586 containing comments on the review of the phased efficacy submission - also contained comments on the FOI summary

8/8/95 - Letter from CVM to INAD 4368 containing comments on the review of the phased efficacy submission, including comments on the FOI summary - also stated that the individual FOI summaries for both the chicken and turkey INAD's could be combined into one

8/25/95 - Letter from CVM (INAD 4853 G0065) addressed comments on the human food section of the FOI, including comments on the submitted toxicology studies and enrofloxacin total residue safe concentrations

12/13/95 - Submission to CVM of a revised FOI Summary - revised to reflect comments received from CVM in their letters dated 11/9/93, 6/14/95 and

8/8/95 and 8/25/95 - also included a summary of the reproductive safety study submitted to CVM on 10/13/95 and additional information on metabolism and residue depletion

8/14/96 - Submission of a revised FOI Summary as an update to the 12/13/95 revision - reformatted in line with a guidance document provided by CVM - Toxicology section was not revised as it had already been reviewed by the Human Food Safety Branch - also the Residue and Metabolism section was not revised as it would be handled by the regulatory reviewer

8/30/96 - Letter from CVM acknowledging the receipt of the revised draft FOI - letter stated that since we had submitted all draft portions of the FOI Summary for which we are responsible, there is no need to submit a draft FOI Summary in the reactivation submission of NADA 140-828

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MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,673,757	173	830	----	06/659,591	06/16/87	10/11/84	04	NO	PAID
2	4,670,444	173	830	----	06/614,923	06/02/87	05/29/84	04	NO	PAID
3	4,672,134	173	830	----	06/744,868	06/09/87	06/14/85	04	NO	PAID
4	4,671,414	173	830	----	06/797,764	06/09/87	11/13/85	04	NO	PAID
5	4,386,953	171	495	----	06/299,919	06/07/83	09/08/81	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	BAYER5899JFW
2	BAYER-5844
3	BAYER55901LH
4	BAYER 5720.1
5	BAYER4895-LH

DIRECT THE RESPONSE TOGETHER WITH ANY QUESTIONS ABOUT THIS NOTICE TO: COMMISSIONER OF PATENTS AND TRADEMARKS, BOX M, FEE, WASHINGTON, DC 20231

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

PAYOR NUMBER
000635

ATTACHMENT "F"

75M3/1201

SPRUNG HORN KRAMER & WOODS
660 WHITE PLAINS ROAD, 4TH FLOOR
TARRYTOWN, NY 10591-5144

DATE MAILED
12/01/94

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,670,444	184	1930	----	06/614,923	06/02/87	05/29/84	08	NO	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER

Bayer 253-KGB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: KLAUS GROHE ET AL.
(Patentee's name)

Patent No.: (number) 4,670,444

Issued: (date) June 2, 1987

For: (title) 7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

BOX PATENT EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

DECLARATION PURSUANT TO 37 C.F.R. §1.740 (a) & (b)

Dear Sir:

I, Kurt G. Briscoe, hereby declare that:

(1) I have been authorized by the owner of record of U.S. Patent No. 4,670,444, namely Bayer Aktiengesellschaft ("Bayer AG") of Leverkusen, Germany, to prepare and file the accompanying Application for Extension of Patent Term Under 35 U.S.C. §156 ("patent term extension application").

(2) I have general authority from Bayer AG to act on behalf of Bayer AG in patent matters.

(3) I have specific authority to act on behalf of Bayer AG in the preparation and filing of the accompanying patent term extension application as supported by the accompanying Associate

Power of Attorney and Change of Correspondence Address.

(4) For the preparation and filing of the patent term extension application, Bayer AG provided me with a copy of the New Animal Drug application ("NADA") filed with the Food and Drug Administration ("FDA") and, also, with a copy of the letter sent from the FDA to Bayer Corporation, the U.S. subsidiary of Bayer AG, approving the NADA.

(5) Based upon the materials provided to me, I prepared the patent term extension application.

(6) I have reviewed and understand the contents of the patent term extension application.

(7) I believe that U.S. Patent No. 4,670,444 is subject to patent term extension pursuant to 35 U.S.C. §1.56 and 37 C.F.R. §1.710.

(8) I believe that an extension of U.S. Patent No. 4,670,444 of the length claimed, i.e., five years, is justified under 35 U.S.C. §156 and the applicable regulations.

(9) I believe U.S. Patent No. 4,670,444 meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

(10) I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: December 3, 1996 By _____
Kurt G. Briscoe

Bayer 253-KGB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: KLAUS GROHE ET AL.
(Patentee's name)

Patent No.: (number) 4,670,444

Issued: (date) June 2, 1987

For: (title) 7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

BOX PATENT EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

CERTIFICATE REGARDING ATTACHED DUPLICATE OF APPLICATION FOR PATENT TERM EXTENSION

Dear Sir:

I, Kurt G. Briscoe, hereby declare that I personally prepared the attached papers, which are listed below:

(1) Application for Extension of Patent Term Under 35 U.S.C. §156;

(2) Attachments A through G thereto;

(3) Declaration Pursuant to 37 C.F.R. §1.740(a) & (b);

and I certify that the attached papers are true and complete duplicates of the original items that accompany this submission.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements

Bayer 253-KGB

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of: KLAUS GROHE ET AL.
(Patentee's name)

Patent No.: (number) 4,670,444

Issued: (date) June 2, 1987

For: (title) 7-AMINO-1-CYCLOPROPYL-4-OXO-1,4-DIHYDRO-QUINOLINE- AND NAPHTHYRIDINE-3-CARBOXYLIC ACIDS AND ANTIBACTERIAL AGENTS CONTAINING THESE COMPOUNDS

BOX PATENT EXTENSION
Commissioner of Patents and Trademarks
Washington, D.C. 20231

ASSOCIATE POWER OF ATTORNEY AND CHANGE OF CORRESPONDENCE ADDRESS

Sir:

The undersigned, Ira J. Schaefer, an attorney of record in Serial No. 06/614,923, filed May 29, 1984, now Patent No. 4,670,444, issued June 2, 1987, hereby appoints Kurt G. Briscoe, Registration No. 33,141, William C. Gerstenzang, Registration No. 27,552, and Mark W. Russell, Registration No. 37,514, associate attorneys, with full power to transact all business in the Patent and Trademark Office connected therewith, including all business connected with the accompanying Application for Patent Term Extension, and requests that all correspondence be directed to Kurt G. Briscoe at:

SPRUNG HORN KRAMER AND WOODS
660 White Plains Road
Tarrytown, New York 10591-5144
(914) 332-1700

Respectfully Submitted,

SPRUNG HORN KRAMER AND WOODS

120 White Plains Road
Tarrytown, New York 10591

By _____
Ira J. Schaefer
Reg. No. 26,802

were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: December 3, 1996

By _____
Kurt G. Briscoe